

Connecting via Winsock to STN

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LOGINID:SSSPTA1642BJF

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

\* \* \* \* \* Welcome to STN International \* \* \* \* \*

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	FEB 28	PATDPAFULL - New display fields provide for legal status data from INPADOC
NEWS	4	FEB 28	BABS - Current-awareness alerts (SDIs) available
NEWS	5	MAR 02	GBFULL: New full-text patent database on STN
NEWS	6	MAR 03	REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS	7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS	8	MAR 22	KOREAPAT now updated monthly; patent information enhanced
NEWS	9	MAR 22	Original IDE display format returns to REGISTRY/ZREGISTRY
NEWS	10	MAR 22	PATDPASPC - New patent database available
NEWS	11	MAR 22	REGISTRY/ZREGISTRY enhanced with experimental property tags
NEWS	12	APR 04	EPFULL enhanced with additional patent information and new fields
NEWS	13	APR 04	EMBASE - Database reloaded and enhanced
NEWS	14	APR 18	New CAS Information Use Policies available online
NEWS	15	APR 25	Patent searching, including current-awareness alerts (SDIs), based on application date in CA/CAPLUS and USPATFULL/USPAT2 may be affected by a change in filing date for U.S. applications.
NEWS	16	APR 28	Improved searching of U.S. Patent Classifications for U.S. patent records in CA/CAPLUS
NEWS	17	MAY 23	GBFULL enhanced with patent drawing images
NEWS	18	MAY 23	REGISTRY has been enhanced with source information from CHEMCATS
NEWS	19	JUN 06	The Analysis Edition of STN Express with Discover! (Version 8.0 for Windows) now available
NEWS	20	JUN 13	RUSSIAPAT: New full-text patent database on STN
NEWS	21	JUN 13	FRFULL enhanced with patent drawing images
NEWS	22	JUN 27	MARPAT displays enhanced with expanded G-group definitions and text labels
NEWS	23	JUL 01	MEDICONF removed from STN
NEWS	24	JUL 07	STN Patent Forums to be held in July 2005
NEWS	25	JUL 13	SCISEARCH reloaded
NEWS	26	JUL 20	Powerful new interactive analysis and visualization software, STN AnaVist, now available
NEWS	27	AUG 11	Derwent World Patents Index(R) web-based training during August
NEWS	28	AUG 11	STN AnaVist workshops to be held in North America
NEWS	EXPRESS		JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005
NEWS	HOURS		STN Operating Hours Plus Help Desk Availability
NEWS	INTER		General Internet Information
NEWS	LOGIN		Welcome Banner and News Items

NEWS PHONE Direct Dial and Telecommunication Network Access to STN  
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005

=> file registry

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 22 AUG 2005 HIGHEST RN 861291-85-2

DICTIONARY FILE UPDATES: 22 AUG 2005 HIGHEST RN 861291-85-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

\*\*\*\*\*  
\*  
\* The CA roles and document type information have been removed from \*  
\* the IDE default display format and the ED field has been added, \*  
\* effective March 20, 2005. A new display format, IDERL, is now \*  
\* available and contains the CA role and document type information. \*  
\*  
\*\*\*\*\*

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:  
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> E "PEG"/CN 25

E1	1	PEFURAZOATE/CN
E2	1	PEFURAZOATE-IKI 220 MIXT./CN
E3	1 -->	PEG/CN
E4	1	PEG (POLYGLYCOL)/CN
E5	1	PEG 100/CN
E6	1	PEG 1000/CN

E7	1	PEG 1000 DIAMINE/CN
E8	1	PEG 1000 MONOSTEARATE/CN
E9	1	PEG 10000/CN
E10	1	PEG 1000MO/CN
E11	1	PEG 1000MS/CN
E12	1	PEG 100MS/CN
E13	1	PEG 11000/CN
E14	1	PEG 115/CN
E15	1	PEG 120 METHYL GLUCOSE DIOLEATE/CN
E16	1	PEG 120 METHYL GLUCOSE TRIOLEATE/CN
E17	1	PEG 12000/CN
E18	1	PEG 13000/CN
E19	1	PEG 1450/CN
E20	1	PEG 150 STEARATE/CN
E21	1	PEG 1500/CN
E22	1	PEG 1500-1,5-PENTANEDIOL-TEREPHTHALIC ACID-TRIMETHYLOLPROPANE COPOLYMER ESTER WITH DODECENYLSUCCINIC ANHYDRIDE/CN
E23	1	PEG 1500-1,5-PENTANEDIOL-TEREPHTHLAIC ACID-TRIMETHYLOLPROPANE COPOLYMER ESTER WITH DODECENYLPHTHALIC ANHYDRIDE/CN
E24	1	PEG 1500-1,5-PENTANEDIOL-TEREPHTHLAIC ACID-TRIMETHYLOLPROPANE COPOLYMER ESTER WITH PHTHALIC ANHYDRIDE/CN
E25	1	PEG 15000/CN

=> S E3

L1 1 PEG/CN

=> DIS L1 1 SQIDE

THE ESTIMATED COST FOR THIS REQUEST IS 6.15 U.S. DOLLARS

DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN

RN 25322-68-3 REGISTRY

CN Poly(oxy-1,2-ethanediyl),  $\alpha$ -hydro- $\omega$ -hydroxy- (9CI) (CA INDEX  
NAME)

OTHER NAMES:

CN	$\alpha,\omega$ -Hydroxypoly(ethylene oxide)
CN	$\alpha$ -Hydro- $\omega$ -hydroxypoly(oxy-1,2-ethanediyl)
CN	$\alpha$ -Hydro- $\omega$ -hydroxypoly(oxyethylene)
CN	1,2-Ethanediol, homopolymer
CN	16600
CN	1660S
CN	400DAB8
CN	Alkox
CN	Alkox E 100
CN	Alkox E 130
CN	Alkox E 160
CN	Alkox E 240
CN	Alkox E 30
CN	Alkox E 30G
CN	Alkox E 45
CN	Alkox E 60
CN	Alkox E 75
CN	Alkox R 100
CN	Alkox R 1000
CN	Alkox R 15
CN	Alkox R 150
CN	Alkox R 400
CN	Alkox SR
CN	Alkox SW
CN	Antarox E 4000
CN	Aquacide III
CN	Aquaffin
CN	Badimol

CN BDH 301  
 CN Bradsyn PEG  
 CN Breox 2000  
 CN Breox 20M  
 CN Breox 4000  
 CN Breox 550  
 CN Breox PEG 300  
 CN CAFO 154  
 CN Carbowax  
 CN Carbowax 100  
 CN Carbowax 1000  
 CN Carbowax 1350  
 CN Carbowax 14000  
 CN Carbowax 1450  
 CN Carbowax 1500  
 CN Carbowax 1540  
 CN Carbowax 20  
 CN Carbowax 200  
 CN Carbowax 20000  
 CN Carbowax 25000  
 CN Carbowax 300  
 CN Carbowax 3350  
 CN **PEG**

ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for  
 DISPLAY

AR 9002-90-8  
 DR 615575-04-7, 12676-74-3, 12770-93-3, 9081-95-2, 9085-02-3, 9085-03-4,  
 174460-08-3, 174460-09-4, 54510-95-1, 125223-68-9, 54847-64-2, 59763-40-5,  
 64441-68-5, 64640-28-4, 133573-31-6, 25104-58-9, 25609-81-8, 134919-43-0,  
 101677-86-5, 99264-61-6, 106186-24-7, 112895-21-3, 114323-93-2,  
 50809-04-6, 50809-59-1, 119219-06-6, 60894-12-4, 61840-14-0, 37361-15-2,  
 112384-37-9, 67411-64-7, 70926-57-7, 75285-02-8, 75285-03-9, 77986-38-0,  
 150872-82-5, 154394-38-4, 79964-26-4, 80341-53-3, 85399-22-0, 85945-29-5,  
 90597-70-9, 88077-80-9, 88747-22-2, 34802-42-1, 107502-63-6, 107529-96-4,  
 116549-90-7, 156948-19-5, 169046-53-1, 188364-77-4, 188924-03-0,  
 189154-62-9, 191743-71-2, 196696-84-1, 201163-43-1, 206357-86-0,  
 221638-71-7, 225502-44-3, 270910-26-4, 307928-07-0, 356055-70-4,  
 391229-98-4

MF (C2 H4 O)n H2 O

CI PMS, COM

PCT Polyether

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS,  
 BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS,  
 CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM\*,  
 DIOGENES, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2, ENCOMPAT, ENCOMPAT2,  
 HSDB\*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK\*, MSDS-OHS, NIOSHTIC,  
 PDLCOM\*, PIRA, PROMT, RTECS\*, SCISEARCH, SPECINFO, TOXCENTER, TULSA,  
 ULIDAT, USAN, USPAT2, USPATFULL, VETU, VTB

(\*File contains numerically searchable property data)

Other Sources: DSL\*\*, TSCA\*\*, WHO

(\*\*Enter CHEMLIST File for up-to-date regulatory information)

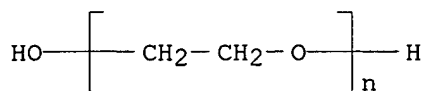
DT.CA Caplus document type: Book; Conference; Dissertation; Journal; Patent; Preprint; Report

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study);  
 CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC  
 (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process);  
 PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role  
 in record)

RLD.P Roles for non-specific derivatives from patents: ANST (Analytical  
 study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC  
 (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process);  
 PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role  
 in record)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

84039 REFERENCES IN FILE CA (1907 TO DATE)  
 22615 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 84192 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file medline  
 COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
6.87	7.08

FULL ESTIMATED COST

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

FILE LAST'UPDATED: 20 AUG 2005 (20050820/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP  
 RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>  
[http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html)

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the  
 MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate  
 substance identification.

=> s l1

L2 185 L1

=> s PEG

9298 PEG  
 747 PEGS

L3 9685 PEG  
 (PEG OR PEGS)

=> s poly () ethylene () glycol

59257 POLY  
 6 POLIES  
 59263 POLY

```

                (POLY OR POLIES)
18961 ETHYLENE
2287 ETHYLENES
19618 ETHYLENE
                (ETHYLENE OR ETHYLENES)
22544 GLYCOL
27720 GLYCOLS
40275 GLYCOL
                (GLYCOL OR GLYCOLS)
L4      2487 POLY (W) ETHYLENE (W) GLYCOL

=> s methoxypoly () ethylene glycol
        66 METHOXYPOLY
18961 ETHYLENE
2287 ETHYLENES
19618 ETHYLENE
                (ETHYLENE OR ETHYLENES)
22544 GLYCOL
27720 GLYCOLS
40275 GLYCOL
                (GLYCOL OR GLYCOLS)
        8421 ETHYLENE GLYCOL
                (ETHYLENE(W) GLYCOL)
L5      52 METHOXYPOLY (W) ETHYLENE GLYCOL

=> s 15 or 14 or 13
L6      10866 L5 OR L4 OR L3

=> s antibod?
L7      694206 ANTIBOD?

=> s clearance or clear or excret? or removed or removal
        89107 CLEARANCE
        5664 CLEARANCES
        91341 CLEARANCE
                (CLEARANCE OR CLEARANCES)
        128624 CLEAR
        549 CLEARS
        129145 CLEAR
                (CLEAR OR CLEARS)
        116634 EXCRET?
        99889 REMOVED
        142890 REMOVAL
        1080 REMOVALS
        143364 REMOVAL
                (REMOVAL OR REMOVALS)
L8      538410 CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL

=> s 18 and 16
L9      1041 L8 AND L6

=> s 19 and 17
L10     129 L9 AND L7

=> s anti-PEG
        574125 ANTI
        6 ANTIS
        574129 ANTI
                (ANTI OR ANTIS)
        9298 PEG
        747 PEGS
        9685 PEG
                (PEG OR PEGS)

```

L11            7 ANTI-PEG  
                 (ANTI(W) PEG)

=> s l11 and l8  
L12            2 L11 AND L8

=> d ibib 1-2

L12 ANSWER 1 OF 2            MEDLINE on STN  
ACCESSION NUMBER:    2002229521            MEDLINE  
DOCUMENT NUMBER:    PubMed ID: 11966757  
TITLE:                The in vivo effects of tumour necrosis factor blockade on  
                      the early cell mediated immune events and syndrome  
                      expression in rat adjuvant arthritis.  
AUTHOR:                Bush K A; Kirkham B W; Walker J S  
CORPORATE SOURCE:    School of Physiology & Pharmacology, University of New  
                      South Wales, NSW, Australia.  
SOURCE:                Clinical and experimental immunology, (2002 Mar) 127 (3)  
                      423-9.  
                      Journal code: 0057202. ISSN: 0009-9104.  
PUB. COUNTRY:        England: United Kingdom  
DOCUMENT TYPE:        Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE:             English  
FILE SEGMENT:        Priority Journals  
ENTRY MONTH:         200209  
ENTRY DATE:           Entered STN: 20020423  
                      Last Updated on STN: 20020906  
                      Entered Medline: 20020904

L12 ANSWER 2 OF 2            MEDLINE on STN  
ACCESSION NUMBER:    2000191525            MEDLINE  
DOCUMENT NUMBER:    PubMed ID: 10725103  
TITLE:                Efficient **clearance** of poly(ethylene  
                      glycol)-modified immunoenzyme with **anti-**  
                      **PEG** monoclonal antibody for prodrug cancer therapy.  
AUTHOR:                Cheng T L; Chen B M; Chern J W; Wu M F; Roffler S R  
CORPORATE SOURCE:    Institute of Biomedical Sciences, Academia Sinica, Taipei,  
                      Taiwan.  
SOURCE:                Bioconjugate chemistry, (2000 Mar-Apr) 11 (2) 258-66.  
                      Journal code: 9010319. ISSN: 1043-1802.  
PUB. COUNTRY:        United States  
DOCUMENT TYPE:        Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE:             English  
FILE SEGMENT:        Priority Journals  
ENTRY MONTH:         200005  
ENTRY DATE:           Entered STN: 20000613  
                      Last Updated on STN: 20000613  
                      Entered Medline: 20000531

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005  
                      E "PEG"/CN 25

L1            1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2            185 S L1  
L3            9685 S PEG  
L4            2487 S POLY ( ) ETHYLENE ( ) GLYCOL  
L5            52 S METHOXPOLY ( ) ETHYLENE GLYCOL

L6 10866 S L5 OR L4 OR L3  
 L7 694206 S ANTIBOD?  
 L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
 L9 1041 S L8 AND L6  
 L10 129 S L9 AND L7  
 L11 7 S ANTI-PEG  
 L12 2 S L11 AND L8

=> s l11 not py>1999  
 3085459 PY>1999  
 L13 3 L11 NOT PY>1999

=> d ibib 1-3

L13 ANSWER 1 OF 3 MEDLINE on STN  
 ACCESSION NUMBER: 1998089627 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 9428158  
 TITLE: Immobilization of L-asparaginase into a biocompatible poly(ethylene glycol)-albumin hydrogel: evaluation of performance in vivo.  
 AUTHOR: Jean-Francois J; D'Urso E M; Fortier G  
 CORPORATE SOURCE: Departement de Chimie-Biochimie, Universite du Quebec, Montreal, Canada.  
 SOURCE: Biotechnology and applied biochemistry, (1997 Dec) 26 ( Pt 3) 203-12.  
 Journal code: 8609465. ISSN: 0885-4513.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199802  
 ENTRY DATE: Entered STN: 19980217  
 Last Updated on STN: 20000303  
 Entered Medline: 19980205

L13 ANSWER 2 OF 3 MEDLINE on STN  
 ACCESSION NUMBER: 84160696 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 6706424  
 TITLE: Polyethylene glycol reactive antibodies in man: titer distribution in allergic patients treated with monomethoxy polyethylene glycol modified allergens or placebo, and in healthy blood donors.  
 AUTHOR: Richter A W; Akerblom E  
 SOURCE: International archives of allergy and applied immunology, (1984) 74 (1) 36-9.  
 Journal code: 0404561. ISSN: 0020-5915.  
 PUB. COUNTRY: Switzerland  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 198405  
 ENTRY DATE: Entered STN: 19900319  
 Last Updated on STN: 19970203  
 Entered Medline: 19840522

L13 ANSWER 3 OF 3 MEDLINE on STN  
 ACCESSION NUMBER: 83107741 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 6401699  
 TITLE: Antibodies against polyethylene glycol produced in animals by immunization with monomethoxy polyethylene glycol modified proteins.  
 AUTHOR: Richter A W; Akerblom E  
 SOURCE: International archives of allergy and applied immunology,



(1983) 70 (2) 124-31.  
Journal code: 0404561. ISSN: 0020-5915.  
PUB. COUNTRY: Switzerland  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198303  
ENTRY DATE: Entered STN: 19900318  
Last Updated on STN: 19900318  
Entered Medline: 19830311

=> d kwic 1

L13 ANSWER 1 OF 3 MEDLINE on STN

AB . . . spleen or liver. ELISA tests at 28 days and 120 days showed the presence of anti-ASNase (and, in lower amounts, **anti-PEG**) antibodies in sera of implanted rats. As observed with other enzyme-immobilization systems used in vivo, the formation of fibroblast-like cell. . .

=> d kwic 2

L13 ANSWER 2 OF 3 MEDLINE on STN

AB . . . allergies and in healthy blood donors employing passive hemagglutination. In untreated allergic patients and in healthy blood donors, naturally occurring **anti-PEG** antibody titers between 32 and 512 were seen in 3.3 and 0.2%, respectively. During hyposensitization with monomethoxy polyethylene glycol modified ragweed extract and honey bee venom, respectively, the patients showed an **anti-PEG** antibody response. Titers of 32-512 were found in 50% of the patients directly after the first treatment course. After 2. . . years of treatment the percentage of patients with such titers declined to 28.5%. Mercaptoethanol treatment of sera indicated that the **anti-PEG** antibodies predominantly were of the IgM isotype. The weak IgM response found in treated patients is considered to be of. . .

=> d kwic 3

L13 ANSWER 3 OF 3 MEDLINE on STN

AB . . . protein and the degree of modification. With modified OA, in the presence of FCA, the majority of animals showed an **anti-PEG** response. With modified SOD and Rag only a small proportion of animals responded. In the absence of FCA, modified OA, given s.c., did not elicit any **anti-PEG** antibody response in rabbits and only a weak response in mice. PEG of MW 10,000 and 100,000 given in FCA. . . mice, showed no or very poor immunogenic properties. Gel diffusion, heterologous passive anaphylaxis and passive hemagglutination were used to demonstrate **anti-PEG** antibodies raised to PEG-modified proteins. Specificity was confirmed by hapten inhibition of precipitation, inhibition of passive hemagglutination and cross-reactivity tests.. . . by PEG of MW 300 it appears that the antigenic determinant of PEG may be a sequence of 6-7 -CH<sub>2</sub>CH<sub>2</sub>O-units. **Anti-PEG** antibodies can be used analytically. By gel diffusion, Peg was detected in minimal concentrations of 0.1-1 microgram/ml. The clinical relevance. . .

=> d ab 3

L13 ANSWER 3 OF 3 MEDLINE on STN

AB Antibodies to polyethylene glycol (PEG) were raised in rabbits by immunization with monomethoxy polyethylene glycol modified ovalbumin (OA), bovine superoxide dismutase (SOD), and ragweed pollen extract (Rag), given in Freund's complete adjuvant (FCA). Immunogenicity depended on the nature of the protein and the degree of modification. With modified OA, in the presence of FCA, the majority of animals showed an **anti-PEG** response. With modified SOD and Rag only a small proportion of animals responded. In the absence of FCA, modified OA, given s.c., did not elicit any **anti-PEG** antibody response in rabbits and only a weak response in mice. PEG of MW 10,000 and 100,000 given in FCA was found nonimmunogenic in rabbits, and PEG of MW  $5.9 \times 10^6$ , given s.c. to mice, showed no or very poor immunogenic properties. Gel diffusion, heterologous passive anaphylaxis and passive hemagglutination were used to demonstrate **anti-PEG** antibodies raised to PEG-modified proteins. Specificity was confirmed by hapten inhibition of precipitation, inhibition of passive hemagglutination and cross-reactivity tests. PEG of MW greater than or equal to 4,000 produced specific precipitates, smaller molecules acted as monovalent haptens. From hapten inhibition of precipitation by PEG of MW 300 it appears that the antigenic determinant of PEG may be a sequence of 6-7  $-\text{CH}_2\text{CH}_2\text{O}-$ units. **Anti-PEG** antibodies can be used analytically. By gel diffusion, Peg was detected in minimal concentrations of 0.1-1 microgram/ml. The clinical relevance of these findings with regard to therapy with PEG-modified enzymes and allergens in humans remains to be established.

=> d kwic

L13 ANSWER 1 OF 3 MEDLINE on STN

AB . . . spleen or liver. ELISA tests at 28 days and 120 days showed the presence of anti-ASNase (and, in lower amounts, **anti-PEG**) antibodies in sera of implanted rats. As observed with other enzyme-immobilization systems used in vivo, the formation of fibroblast-like cell. . .

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005

E "PEG"/CN 25

L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2 185 S L1

L3 9685 S PEG

L4 2487 S POLY ( ) ETHYLENE ( ) GLYCOL

L5 52 S METHOXPOLY ( ) ETHYLENE GLYCOL

L6 10866 S L5 OR L4 OR L3

L7 694206 S ANTIBOD?

L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL

L9 1041 S L8 AND L6

L10 129 S L9 AND L7

L11 7 S ANTI-PEG

L12 2 S L11 AND L8

L13 3 S L11 NOT PY>1999

=> s l10 not py>1999

3085459 PY>1999

L14 97 L10 NOT PY>1999

=> s l14 not py>1998  
3546810 PY>1998  
L15 90 L14 NOT PY>1998

=> s increase? or accelerat?  
1841898 INCREASE?  
88142 ACCELERAT?  
L16 1898836 INCREASE? OR ACCELERAT?

=> s l16 and l15  
L17 24 L16 AND L15

=> s l16 (S) l8  
L18 51664 L16 (S) L8

=> s l18 and l17  
L19 7 L18 AND L17

=> d ibib 1-4

L19 ANSWER 1 OF 7 MEDLINE on STN  
ACCESSION NUMBER: 1998151177 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 9492213  
TITLE: Improved local delivery of TGF-beta2 by binding to  
injectable fibrillar collagen via difunctional polyethylene  
glycol.  
AUTHOR: Bentz H; Schroeder J A; Estridge T D  
CORPORATE SOURCE: Research and Development, Collagen Corporation, Palo Alto,  
California 94303, USA.  
SOURCE: Journal of biomedical materials research, (1998 Mar 15) 39  
(4) 539-48.  
Journal code: 0112726. ISSN: 0021-9304.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199804  
ENTRY DATE: Entered STN: 19980422  
Last Updated on STN: 19980422  
Entered Medline: 19980413

L19 ANSWER 2 OF 7 MEDLINE on STN  
ACCESSION NUMBER: 97415461 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 9271260  
TITLE: Immunogenicity and pharmacokinetic attributes of  
**poly(ethylene glycol)**-grafted  
immunoliposomes.  
AUTHOR: Harding J A; Engbers C M; Newman M S; Goldstein N I;  
Zalipsky S  
CORPORATE SOURCE: SEQUUS Pharmaceuticals, Incorporated, Menlo Park, CA 94025,  
USA.  
SOURCE: Biochimica et biophysica acta, (1997 Jul 25) 1327 (2)  
181-92.  
Journal code: 0217513. ISSN: 0006-3002.  
PUB. COUNTRY: Netherlands  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199709  
ENTRY DATE: Entered STN: 19970926  
Last Updated on STN: 20000303  
Entered Medline: 19970918

L19 ANSWER 3 OF 7 MEDLINE on STN  
 ACCESSION NUMBER: 95071855 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 7981064  
 TITLE: The potential for enhanced tumour localisation by  
**poly(ethylene glycol)**  
 modification of anti-CEA **antibody**.  
 AUTHOR: Pedley R B; Boden J A; Boden R; Begent R H; Turner A;  
 Haines A M; King D J  
 CORPORATE SOURCE: Department of Clinical Oncology, Royal Free Hospital School  
 of Medicine, London, U.K.  
 SOURCE: British journal of cancer, (1994 Dec) 70 (6) 1126-30.  
 Journal code: 0370635. ISSN: 0007-0920.  
 PUB. COUNTRY: SCOTLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199501  
 ENTRY DATE: Entered STN: 19950116  
 Last Updated on STN: 19980206  
 Entered Medline: 19950103

L19 ANSWER 4 OF 7 MEDLINE on STN  
 ACCESSION NUMBER: 92235285 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 1569204  
 TITLE: IgG **antibody** response to polyethylene  
 glycol-modified adenosine deaminase in patients with  
 adenosine deaminase deficiency.  
 AUTHOR: Chaffee S; Mary A; Stiehm E R; Girault D; Fischer A;  
 Hershfield M S  
 CORPORATE SOURCE: Department of Medicine, Duke University Medical Center,  
 Durham, North Carolina 27710.  
 CONTRACT NUMBER: DK20902 (NIDDK)  
 SOURCE: Journal of clinical investigation, (1992 May) 89 (5)  
 1643-51.  
 Journal code: 7802877. ISSN: 0021-9738.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 199205  
 ENTRY DATE: Entered STN: 19920612  
 Last Updated on STN: 19920612  
 Entered Medline: 19920526

=> d kwic 3

L19 ANSWER 3 OF 7 MEDLINE on STN  
 TI The potential for enhanced tumour localisation by **poly(ethylene glycol)** modification of anti-CEA **antibody**.  
 AB Attachment of **poly(ethylene glycol)** (**PEG**) to proteins can greatly alter their pharmacological properties, including extending the plasma half-life and reducing immunogenicity, both of which are potentially beneficial to tumour targeting. IgG, F(ab')<sub>2</sub> and Fab' fragments of the anti-CEA **antibody** A5B7 were chemically modified with **PEG** (M(r) 5,000), labelled with <sup>125</sup>I and their pharmacokinetics compared with the unmodified forms in the LS174T colonic xenograft in nude mice. **PEG** modification of the intact **antibody** had little effect on biodistribution, although tumour localisation was slightly reduced. In contrast, similar modification of F(ab')<sub>2</sub> and Fab'A5B7 significantly prolonged plasma half-life and **increased**

radioantibody accumulation in the tumour and to a lesser extent in normal tissues, but reduced tissue to blood ratios. Prior to modification, Fab' A5B7 (M(r) 50,000) cleared more rapidly from the circulation than F(ab')<sub>2</sub> (M(r) 100,000), but after PEG attachment their biodistributions converged, while the tumour to blood ratios were reduced and resembled that of the intact **antibody**. The enhanced tumour accumulation, reduced normal tissue to blood ratios and potentially reduced immunogenicity of fragments after PEG attachment may therefore prove superior to either unmodified fragments or intact **antibody** for **antibody**-targeted therapy, although the **increased** plasma half-life may necessitate the use of a **clearance** mechanism.

CT Check Tags: In Vitro

\*Adenocarcinoma: IM, immunology  
Animals

**Antibodies, Monoclonal: CH, chemistry**

**\*Antibodies, Monoclonal: ME, metabolism**

\*Carcinoembryonic Antigen: IM, immunology

\*Colonic Neoplasms: IM, immunology

Humans

Immunoglobulins, Fab: ME, metabolism

Mice

Mice, Nude

Neoplasm. . .

CN 0 (**Antibodies, Monoclonal**); 0 (Carcinoembryonic Antigen); 0 (Immunoglobulins, Fab); 0 (Polyethylene Glycols)

=> d kwic ibib 3

L19 ANSWER 3 OF 7 MEDLINE on STN

TI The potential for enhanced tumour localisation by **poly(ethylene glycol)** modification of anti-CEA **antibody**.

AB Attachment of **poly(ethylene glycol)** (**PEG**) to proteins can greatly alter their pharmacological properties, including extending the plasma half-life and reducing immunogenicity, both of which are potentially beneficial to tumour targeting. IgG, F(ab')<sub>2</sub> and Fab' fragments of the anti-CEA **antibody** A5B7 were chemically modified with **PEG** (M(r) 5,000), labelled with <sup>125</sup>I and their pharmacokinetics compared with the unmodified forms in the LS174T colonic xenograft in nude mice. **PEG** modification of the intact **antibody** had little effect on biodistribution, although tumour localisation was slightly reduced. In contrast, similar modification of F(ab')<sub>2</sub> and Fab'A5B7 significantly prolonged plasma half-life and **increased** radioantibody accumulation in the tumour and to a lesser extent in normal tissues, but reduced tissue to blood ratios. Prior to modification, Fab' A5B7 (M(r) 50,000) cleared more rapidly from the circulation than F(ab')<sub>2</sub> (M(r) 100,000), but after **PEG** attachment their biodistributions converged, while the tumour to blood ratios were reduced and resembled that of the intact **antibody**. The enhanced tumour accumulation, reduced normal tissue to blood ratios and potentially reduced immunogenicity of fragments after **PEG** attachment may therefore prove superior to either unmodified fragments or intact **antibody** for **antibody**-targeted therapy, although the **increased** plasma half-life may necessitate the use of a **clearance** mechanism.

CT Check Tags: In Vitro

\*Adenocarcinoma: IM, immunology  
Animals

**Antibodies, Monoclonal: CH, chemistry**

**\*Antibodies, Monoclonal: ME, metabolism**

\*Carcinoembryonic Antigen: IM, immunology

\*Colonic Neoplasms: IM, immunology

Humans

Immunoglobulins, Fab: ME, metabolism

Mice

Mice, Nude

Neoplasm. . .

CN . 0 (**Antibodies**, Monoclonal); 0 (Carcinoembryonic Antigen); 0  
(Immunoglobulins, Fab); 0 (Polyethylene Glycols)

ACCESSION NUMBER: 95071855 MEDLINE

DOCUMENT NUMBER: PubMed ID: 7981064

TITLE: The potential for enhanced tumour localisation by  
**poly(ethylene glycol)**

modification of anti-CEA **antibody**.

AUTHOR: Pedley R B; Boden J A; Boden R; Begent R H; Turner A;  
Haines A M; King D J

CORPORATE SOURCE: Department of Clinical Oncology, Royal Free Hospital School  
of Medicine, London, U.K.

SOURCE: British journal of cancer, (1994 Dec) 70 (6) 1126-30.  
Journal code: 0370635. ISSN: 0007-0920.

PUB. COUNTRY: SCOTLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199501

ENTRY DATE: Entered STN: 19950116

Last Updated on STN: 19980206

Entered Medline: 19950103

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005

E "PEG"/CN 25

L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2 185 S L1

L3 9685 S PEG

L4 2487 S POLY ( ) ETHYLENE ( ) GLYCOL

L5 52 S METHOXPOLY ( ) ETHYLENE GLYCOL

L6 10866 S L5 OR L4 OR L3

L7 694206 S ANTIBOD?

L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL

L9 1041 S L8 AND L6

L10 129 S L9 AND L7

L11 7 S ANTI-PEG

L12 2 S L11 AND L8

L13 3 S L11 NOT PY>1999

L14 97 S L10 NOT PY>1999

L15 90 S L14 NOT PY>1998

L16 1898836 S INCREASE? OR ACCELERAT?

L17 24 S L16 AND L15

L18 51664 S L16 (S) L8

L19 7 S L18 AND L17

=> d ibib 5-7

L19 ANSWER 5 OF 7 MEDLINE on STN

ACCESSION NUMBER: 91334430 MEDLINE

DOCUMENT NUMBER: PubMed ID: 1714590

TITLE: Use of site-directed mutagenesis to enhance the epitope-shielding effect of covalent modification of proteins with polyethylene glycol.  
 AUTHOR: Hershfield M S; Chaffee S; Koro-Johnson L; Mary A; Smith A A; Short S A  
 CORPORATE SOURCE: Department of Medicine, Duke University Medical Center, Durham, NC 27710.  
 CONTRACT NUMBER: DK20902 (NIDDK)  
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1991 Aug 15) 88 (16) 7185-9. Journal code: 7505876. ISSN: 0027-8424.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 OTHER SOURCE: GENBANK-M60917; GENBANK-M66858; GENBANK-M66859; GENBANK-M66860; GENBANK-M66861; GENBANK-M66862; GENBANK-S45955; GENBANK-S45957; GENBANK-S45959; GENBANK-S49265  
 ENTRY MONTH: 199109  
 ENTRY DATE: Entered STN: 19911006  
 Last Updated on STN: 19960129  
 Entered Medline: 19910918

L19 ANSWER 6 OF 7 MEDLINE on STN  
 ACCESSION NUMBER: 89391643 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 2789501  
 TITLE: Low avidity **antibodies** to double stranded DNA in systemic lupus erythematosus: a longitudinal study of their clinical significance.  
 AUTHOR: Nossent J C; Huysen V; Smeenk R J; Swaak A J  
 CORPORATE SOURCE: Department of Rheumatology, Dr Daniel den Hoed Clinic, Rotterdam, The Netherlands.  
 SOURCE: Annals of the rheumatic diseases, (1989 Aug) 48 (8) 677-82. Journal code: 0372355. ISSN: 0003-4967.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 198910  
 ENTRY DATE: Entered STN: 19900309  
 Last Updated on STN: 19900309  
 Entered Medline: 19891020

L19 ANSWER 7 OF 7 MEDLINE on STN  
 ACCESSION NUMBER: 85003720 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 6479199  
 TITLE: Association of circulating immune complexes with glomerular proteinuria in patients with transitional cell carcinoma of the urinary bladder.  
 AUTHOR: Skaarup P; Jensenius J C; Brandslund I; Svehag S E; Wolf H  
 SOURCE: European urology, (1984) 10 (4) 249-53. Journal code: 7512719. ISSN: 0302-2838.  
 PUB. COUNTRY: Switzerland  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 198411  
 ENTRY DATE: Entered STN: 19900320  
 Last Updated on STN: 19900320  
 Entered Medline: 19841101

=> d kwic 1

L19 ANSWER 1 OF 7 MEDLINE on STN

AB To overcome rapid diffusion and **clearance** from the implant site and to **increase** stability, recombinant transforming growth factor beta2 (TGF-beta2) was covalently bound to injectable bovine dermal fibrillar collagen (FC) and its activity. . . to admixed TGF-beta2. Covalent binding was achieved in a two-step procedure: First, TGF-beta2 was reacted with the difunctional polyethylene glycol (**PEG**) linker, and then the **PEG**-attached TGF-beta2 (**PEG**-TGF-beta2) was bound to the fibrillar collagen (**FC-PEG**-TGF-beta2). Initial binding of TGF-beta2 to difunctional succinimidyl glutarate (D-SG-**PEG**) or succinimidyl propionate polyethylene glycol (D-SE-**PEG**) linkers was completed after reacting for 8 or 10 min as monitored by reverse-phase high-performance liquid chromatography. After reaction with injectable fibrillar collagen, extraction of unbound **PEG**-TGF-beta2 and Western blot analysis, using a TGF-beta specific **antibody**, demonstrated that at least 85% of the TGF-beta2 was bound to the fibrillar collagen. The activity of **PEG**-TGF-beta2 was fully stable in phosphate-buffered saline at 4 degrees C and 37 degrees C for at least up to 4. . . inactivated after 1 week of incubation, as measured by the mink lung epithelial cell (Mv1Lu) growth inhibition assay. Formulations of **FC-PEG**-TGF-beta2 containing 40 microg/ mL TGF-beta2 were implanted subcutaneously into rats and analyzed after days 7, 21, and 42. All TGF-beta2-containing. . . the TGF-beta typical fibroblastic response at the day 7 time point. Covalent binding of TGF-beta2 to collagen with both difunctional **PEG** crosslinkers resulted in a significantly stronger and longer-lasting TGF-beta2 response than that observed with admixed formulations of collagen and TGF-beta. The TGF-beta response with **FC-PEG**-TGF-beta2 lasted up to day 42 but was not seen after day 7 for TGF-beta2 admixed to FC. These findings clearly demonstrate that TGF-beta2 remains fully active after being covalently bound to collagen via difunctional **PEG**. In addition, covalent binding potentiates and prolongs in vivo TGF-beta responses and stabilizes the TGF-beta in vitro. Results suggest that. . .

=> d kwic 2

L19 ANSWER 2 OF 7 MEDLINE on STN

TI Immunogenicity and pharmacokinetic attributes of **poly(ethylene glycol)**-grafted immunoliposomes.

AB Immunoliposomes composed of hydrogenated soy phosphatidylcholine, cholesterol, **methoxypoly(ethylene glycol)**-distearoyl phosphatidylethanolamine (mPEG-DSPE), and hydrazide-**PEG**-DSPE (mole ratio, 57:38:3.3:1.7) linked to periodate-oxidized chimerized mouse IgG (C225, anti-human epidermal growth factor receptor) were prepared by an optimized. . . (MRT = 8.5 h, Cl = 0.2 ml/h). Subsequent injections of the immunoliposomes into the same animals resulted in rapid **clearance** (MRT < or = 0.7 h, Cl > or = 7 ml/h), which was accompanied by a significant **increase** in anti-C225 specific titers. Upon repeated injection or coinjection with the parent liposomes free C225 consistently exhibited prolonged circulation without any **increase** in C225-specific antisera, but was cleared quickly when administered into animals that had been pretreated with the immunoliposomes. Screening of. . . the immune response was specifically triggered by the constant human region of C225. These results demonstrate that the preparations of **PEG**-grafted immunoliposomes are more immunogenic than the free IgG component, which is of profound importance to the **antibody**-mediated liposomal drug delivery effort.

CT Check Tags: Male



Animals

Antibodies, Monoclonal: AD, administration & dosage

Antibodies, Monoclonal: IM, immunology

\*Drug Delivery Systems

Enzyme-Linked Immunosorbent Assay

Flow Cytometry

Humans

Immunoglobulins, Fab: ME, metabolism

\*Liposomes: IM, immunology

CN 0 (Antibodies, Monoclonal); 0 (Immunoglobulins, Fab); 0  
(Liposomes); 0 (Phosphatidylethanolamines); 0 (Polyethylene Glycols); EC  
2.7.1.112 (Receptor, Epidermal Growth Factor)

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

9.14

16.22

FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005

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FILE COVERS 1907 - 23 Aug 2005 VOL 143 ISS 9

FILE LAST UPDATED: 22 Aug 2005 (20050822/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s PEG

33003 PEG

1125 PEGS

L20 33476 PEG

(PEG OR PEGS)

=> s poly () ethylene () glycol

644812 POLY

2 POLIES

644813 POLY

(POLY OR POLIES)

506522 ETHYLENE

3337 ETHYLENES

507988 ETHYLENE

(ETHYLENE OR ETHYLENES)

334892 GLYCOL

44021 GLYCOLS

349919 GLYCOL

(GLYCOL OR GLYCOLS)

```

L21      12996 POLY (W) ETHYLENE (W) GLYCOL

=> s methoxypoly () ethylene glycol
      228 METHOXPOLY
      506522 ETHYLENE
      3337 ETHYLENES
      507988 ETHYLENE
            (ETHYLENE OR ETHYLENES)
      334892 GLYCOL
      44021 GLYCOLS
      349919 GLYCOL
            (GLYCOL OR GLYCOLS)
      122310 ETHYLENE GLYCOL
            (ETHYLENE(W) GLYCOL)
L22      144 METHOXPOLY (W) ETHYLENE GLYCOL

=> s l22 or l21 or l20
L23      41717 L22 OR L21 OR L20

=> s antibod?
L24      440322 ANTIBOD?

=> s clearance or clear or excret? or removed or removal
      67750 CLEARANCE
      5064 CLEARANCES
      69883 CLEARANCE
            (CLEARANCE OR CLEARANCES)
      191308 CLEAR
      942 CLEARS
      192117 CLEAR
            (CLEAR OR CLEARS)
      158408 EXCRET?
      390380 REMOVED
      620820 REMOVAL
      5047 REMOVALS
      622011 REMOVAL
            (REMOVAL OR REMOVALS)
L25      1304988 CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL

=> s clearance or clear? or excret? or removed or removal
      67750 CLEARANCE
      5064 CLEARANCES
      69883 CLEARANCE
            (CLEARANCE OR CLEARANCES)
      422339 CLEAR?
      158408 EXCRET?
      390380 REMOVED
      620820 REMOVAL
      5047 REMOVALS
      622011 REMOVAL
            (REMOVAL OR REMOVALS)
L26      1459976 CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL

=> s increase? or accelerat?
      3483178 INCREASE?
      330235 ACCELERAT?
L27      3736368 INCREASE? OR ACCELERAT?
      75% OF LIMIT FOR TOTAL ANSWERS REACHED

=> s l26 (S) l27
L28      99738 L26 (S) L27

=> s l24 and l28

```

L29 1750 L24 AND L28

=> s 129 and 123

L30 16 L29 AND L23

=> s anti-PEG

378223 ANTI

9 ANTIS

378230 ANTI

(ANTI OR ANTIS)

33003 PEG

1125 PEGS

33476 PEG

(PEG OR PEGS)

L31 9 ANTI-PEG

(ANTI(W) PEG)

=> s 131 not py>1999

5788970 PY>1999

L32 3 L31 NOT PY>1999

=> d ibib 1-3

L32 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:239090 CAPLUS

DOCUMENT NUMBER: 131:63325

TITLE: Accelerated Clearance of Polyethylene Glycol-Modified Proteins by Anti-Polyethylene Glycol IgM

AUTHOR(S): Cheng, Tian-Lu; Wu, Pin-Yi; Wu, Ming-Fang; Chern, Ji-Wang; Roffler, Steve R.

CORPORATE SOURCE: Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan

SOURCE: Bioconjugate Chemistry (1999), 10(3), 520-528

CODEN: BCCHE; ISSN: 1043-1802

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:24552 CAPLUS

DOCUMENT NUMBER: 128:162592

TITLE: Immobilization of L-asparaginase into a biocompatible poly(ethylene glycol)-albumin hydrogel: evaluation of performance in vivo

AUTHOR(S): Jean-Francois, Jacques; D'urso, Edith Marie; Fortier, Guy

CORPORATE SOURCE: Laboratoire d'Enzymologie Appliquee, Departement de Chimie-Biochimie, Universite du Quebec, Montreal, Montreal, QC, H3C 3P8, Can.

SOURCE: Biotechnology and Applied Biochemistry (1997), 26(3), 203-212

CODEN: BABIE; ISSN: 0885-4513

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1983:15249 CAPLUS

DOCUMENT NUMBER: 98:15249

TITLE: Antibodies against polyethylene glycol produced in animals by immunization with monomethoxy polyethylene glycol-modified proteins  
AUTHOR(S): Richter, Ary Wolfgang; Aakerblom, Eva  
CORPORATE SOURCE: Dep. Biomed. Res., Pharm. AB, Uppsala, 75104, Swed.  
SOURCE: International Archives of Allergy and Applied Immunology (1983), 70(2), 124-31  
CODEN: IAAAAM; ISSN: 0020-5915  
DOCUMENT TYPE: Journal  
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005  
E "PEG"/CN 25

L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2 185 S L1  
L3 9685 S PEG  
L4 2487 S POLY ( ) ETHYLENE ( ) GLYCOL  
L5 52 S METHOXPOLY ( ) ETHYLENE GLYCOL  
L6 10866 S L5 OR L4 OR L3  
L7 694206 S ANTIBOD?  
L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L9 1041 S L8 AND L6  
L10 129 S L9 AND L7  
L11 7 S ANTI-PEG  
L12 2 S L11 AND L8  
L13 3 S L11 NOT PY>1999  
L14 97 S L10 NOT PY>1999  
L15 90 S L14 NOT PY>1998  
L16 1898836 S INCREASE? OR ACCELERAT?  
L17 24 S L16 AND L15  
L18 51664 S L16 (S) L8  
L19 7 S L18 AND L17

FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005

L20 33476 S PEG  
L21 12996 S POLY ( ) ETHYLENE ( ) GLYCOL  
L22 144 S METHOXPOLY ( ) ETHYLENE GLYCOL  
L23 41717 S L22 OR L21 OR L20  
L24 440322 S ANTIBOD?  
L25 1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L26 1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L27 3736368 S INCREASE? OR ACCELERAT?  
L28 99738 S L26 (S) L27  
L29 1750 S L24 AND L28  
L30 16 S L29 AND L23  
L31 9 S ANTI-PEG  
L32 3 S L31 NOT PY>1999

=> s l30 not py>1998  
6611305 PY>1998

L33 6 L30 NOT PY>1998

=> d ibib 1-3

L33 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1998:90995 CAPLUS

DOCUMENT NUMBER: 128:196557  
TITLE: Improved local delivery of TGF- $\beta$ 2 by binding to injectable fibrillar collagen via difunctional polyethylene glycol  
AUTHOR(S): Bentz, H.; Schroeder, J. A.; Estridge, T. D.  
CORPORATE SOURCE: Research and Development, Collagen Corporation, Palo Alto, CA, 94303, USA  
SOURCE: Journal of Biomedical Materials Research (1998), 39(4), 539-548  
CODEN: JBMRBG; ISSN: 0021-9304  
PUBLISHER: John Wiley & Sons, Inc.  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1997:463486 CAPLUS  
DOCUMENT NUMBER: 127:99686  
TITLE: Immunogenicity-pharmacokinetics relationship of polyethylene glycol-grafted immunoliposomes  
AUTHOR(S): Zalipsky, S.; Harding, J. A.; Engbers, C. M.; Newman, M. S.; Goldstein, N. I.  
CORPORATE SOURCE: SEQUUS Pharmaceuticals, Inc., Menlo Park, CA, 94025, USA  
SOURCE: Proceedings of the International Symposium on Controlled Release of Bioactive Materials (1997), 24th, 87-88  
CODEN: PCRMEY; ISSN: 1022-0178  
PUBLISHER: Controlled Release Society, Inc.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

L33 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1997:420003 CAPLUS  
DOCUMENT NUMBER: 127:140290  
TITLE: Immunogenicity and pharmacokinetic attributes of **poly(ethylene glycol)**-grafted immunoliposomes  
AUTHOR(S): Harding, Jennifer A.; Engbers, Charles M.; Newman, Mary S.; Goldstein, Neil I.; Zalipsky, Samuel  
CORPORATE SOURCE: SEQUUS Pharmaceuticals, Incorporated, 960 Hamilton Court, Menlo Park, USA  
SOURCE: Biochimica et Biophysica Acta (1997), 1327(2), 181-192  
CODEN: BBACAQ; ISSN: 0006-3002  
PUBLISHER: Elsevier  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d kwic 2

L33 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
AB Preps. of site-specifically constructed, aggregation free **PEG**-grafted immunoliposomes are more immunogenic than free C225 **antibodies** (Ab). This immunogenicity potentiation was almost entirely due to the constant human Fc region of the Ab. Presence of C225-specific Ab's in the immunoliposome-treated rats dramatically **accelerated clearance** of subsequently injected immunoliposomes or free C225. Negligible response to the Fab portion of conjugated C225 was detected, suggesting that use of Fab' as a targeting

moiety on **PEG**-liposomes is less likely to cause immunogenicity related problems. These observations are of importance to **antibody**-mediated liposomal drug delivery.

ST immunoliposome **PEG** grafted **antibody**

IT Epidermal growth factor receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study) (**antibodies** to; immunogenicity-pharmacokinetics relationship of polyethylene glycol-grafted immunoliposomes)

IT Polyoxyalkylenes, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (derivs., conjugates with C225 **antibody**; immunogenicity-pharmacokinetics relationship of polyethylene glycol-grafted immunoliposomes)

IT **Antibodies**

RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (to EGF receptor, conjugates with **PEG** derivs.; immunogenicity-pharmacokinetics relationship of polyethylene glycol-grafted immunoliposomes)

IT 25322-68-3D, **Peg**, derivs., conjugates with C225 **antibody**

171115-99-4D, derivs., conjugates with C225 **antibody**

178744-28-0D, derivs., conjugates with C225 **antibody**

RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (immunogenicity-pharmacokinetics relationship of polyethylene glycol-grafted immunoliposomes)

=> d kwic 3

L33 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN

TI Immunogenicity and pharmacokinetic attributes of **poly(ethylene glycol)**-grafted immunoliposomes

AB Immunoliposomes composed of hydrogenated soy phosphatidylcholine, cholesterol, **methoxypoly(ethylene glycol)**-distearoyl phosphatidylethanolamine (mPEG-DSPE), and hydrazide-**PEG**-DSPE (mole ratio, 57:38:3.3:1.7) linked to periodate-oxidized chimerized mouse IgG (C225, anti-human epidermal growth factor receptor) were prepared by an optimized. . . (MRT = 8.5 h, Cl = 0.2 mL/h). Subsequent injections of the immunoliposomes into the same animals resulted in rapid **clearance** (MRT≤0.7 h, Cl≥7 mL/h), which was accompanied by a significant **increase** in anti-C225 specific titers. Upon repeated injection or coinjection with the parent liposomes free C225 consistently exhibited prolonged circulation without any **increase** in C225-specific antisera, but was **cleared** quickly when administered into animals that had been pretreated with the immunoliposomes. Screening of the immunoliposome induced antisera against human. . . the immune response was specifically triggered by the constant human region of C225. These results demonstrate that the preps. of **PEG**-grafted immunoliposomes are more immunogenic than the free IgG component, which is of profound importance to the **antibody**-mediated liposomal drug delivery effort.

ST immunoliposome **PEG** grafted; pharmacokinetics immunoliposome **PEG** grafted

IT Immunoglobulins

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (G; immunogenicity and pharmacokinetic attributes of **poly(ethylene glycol)**-grafted immunoliposomes)

IT Epidermal growth factor receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (antibodies to; immunogenicity and pharmacokinetic attributes  
 of **poly(ethylene glycol)**-grafted  
 immunoliposomes)

IT Phosphatidylcholines, biological studies  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); PEP (Physical, engineering or chemical process); THU  
 (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
 (immunogenicity and pharmacokinetic attributes of **poly(**  
**ethylene glycol)**-grafted immunoliposomes)

IT Drug delivery systems  
 (immunoliposomes; immunogenicity and pharmacokinetic attributes of  
**poly(ethylene glycol)**-grafted  
 immunoliposomes)

IT Polyoxyalkylenes, biological studies  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);  
 BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (reaction products with distearoylphosphatidylethanolamine, hydrazide  
 derivative; immunogenicity and pharmacokinetic attributes of **poly**  
**(ethylene glycol)**-grafted immunoliposomes)

IT 4537-76-2DP, Distearoylphosphatidylethanolamine, reaction products with  
**PEG** derivs. 9004-74-4DP, Methoxypolyethylene glycol, reaction  
 products with distearoylphosphatidylethanolamine 25322-68-3DP,  
**PEG**, reaction products with distearoylphosphatidylethanolamine,  
 hydrazide derivative  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);  
 BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (immunogenicity and pharmacokinetic attributes of **poly(**  
**ethylene glycol)**-grafted immunoliposomes)

=> d ibib 4-6

L33 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 1995:292108 CAPLUS  
 DOCUMENT NUMBER: 122:75593  
 TITLE: The potential for enhanced tumor localization by  
**poly(ethylene glycol)**  
 modification of anti-CEA **antibody**

AUTHOR(S): Pedley, R. B.; Boden, J. A.; Boden, R.; Begent, R. H.  
 J.; Turner, A.; Haines, A. M. R.; King, D. J.

CORPORATE SOURCE: Department Clinical Oncology, Royal Free Hospital  
 School Medicine, London, NW3 2PF, UK

SOURCE: British Journal of Cancer (1994), 70(6), 1126-30  
 CODEN: BJCAAI; ISSN: 0007-0920

DOCUMENT TYPE: Journal  
 LANGUAGE: English

L33 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 1993:250975 CAPLUS  
 DOCUMENT NUMBER: 118:250975  
 TITLE: Radioimmunoassay for the pyridinoline crosslinked  
 carboxy-terminal telopeptide of type I collagen: a new  
 serum marker of bone collagen degradation

AUTHOR(S): Risteli, Juha; Elomaa, Inkeri; Niemi, Seija; Novamo,  
 Anne; Risteli, Leila

CORPORATE SOURCE: Dep. Med. Biochem., Univ. Oulu, Oulu, SF-90220,  
 Finland

SOURCE: Clinical Chemistry (Washington, DC, United States)  
 (1993), 39(4), 635-40  
 CODEN: CLCHAU; ISSN: 0009-9147

DOCUMENT TYPE: Journal  
LANGUAGE: English

L33 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1991:550137 CAPLUS

DOCUMENT NUMBER: 115:150137

TITLE: Use of site-directed mutagenesis to enhance the  
epitope-shielding effect of covalent modification of  
proteins with polyethylene glycol

AUTHOR(S): Hershfield, Michael S.; Chaffee, Sara; Koro-Johnson,  
Lillian; Mary, Ann; Smith, Albert A.; Short, Steven A.

CORPORATE SOURCE: Med. Cent., Duke Univ., Durham, NC, 27710, USA

SOURCE: Proceedings of the National Academy of Sciences of the  
United States of America (1991), 88(16), 7185-9

CODEN: PNASA6; ISSN: 0027-8424

DOCUMENT TYPE: Journal

LANGUAGE: English

=> file pctfull

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	62.60	78.82

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.46	-1.46

FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005

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FILE LAST UPDATED: 22 AUG 2005 <20050822/UP>

MOST RECENT UPDATE WEEK: 200533 <200533/EW>

FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

=> s PEG

33330 PEG

4725 PEGS

L34 35377 PEG

(PEG OR PEGS)

=> s poly () ethylene () glycol

106749 POLY

281 POLIES

107011 POLY

(POLY OR POLIES)

94414 ETHYLENE

486 ETHYLENES

94496 ETHYLENE

(ETHYLENE OR ETHYLENES)

99346 GLYCOL

38678 GLYCOLS

106001 GLYCOL

(GLYCOL OR GLYCOLS)

L35 5321 POLY (W) ETHYLENE (W) GLYCOL

=> s methoxypoly () ethylene glycol

179 METHOXPOLY

94414 ETHYLENE

486 ETHYLENES

94496 ETHYLENE



```

          (ETHYLENE OR ETHYLENES)
    99346 GLYCOL
    38678 GLYCOLS
    106001 GLYCOL
          (GLYCOL OR GLYCOLS)
    34591 ETHYLENE GLYCOL
          (ETHYLENE(W) GLYCOL)
L36      76 METHOXYPOLY (W) ETHYLENE GLYCOL

=> s antibod?
L37      80487 ANTIBOD?

=> s clearance or clear? or excret? or removed or removal
    40394 CLEARANCE
    3516 CLEARANCES
    41825 CLEARANCE
          (CLEARANCE OR CLEARANCES)
    285091 CLEAR?
    16591 EXCRET?
    339076 REMOVED
    14 REMOVEDS
    339079 REMOVED
          (REMOVED OR REMOVEDS)
    186688 REMOVAL
    807 REMOVALS
    186876 REMOVAL
          (REMOVAL OR REMOVALS)
L38      492783 CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL

```

```

=> s increase? or accelerat?
    477801 INCREASE?
    83290 ACCELERAT?
L39      496097 INCREASE? OR ACCELERAT?

```

```

=> s l38 (S) l39
L40      83462 L38 (S) L39

```

```

=> s anti-PEG
    159836 ANTI
    158 ANTIS
    159865 ANTI
          (ANTI OR ANTIS)
    33330 PEG
    4725 PEGS
    35377 PEG
          (PEG OR PEGS)
L41      7 ANTI-PEG
          (ANTI(W) PEG)

```

```

=> s l41 and l40
L42      5 L41 AND L40

```

```

=> d ibib 1-3

```

```

L42      ANSWER 1 OF 5      PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:          2005072385 PCTFULL   ED 20050816   EW 200532
TITLE (ENGLISH):          PITUITARY ADENYLATE CYCLASE ACTIVATING PEPTIDE (PACAP)
                           RECEPTOR (VPAC2) AGONISTS AND THEIR PHARMACOLOGICAL
                           METHODS OF USE
TITLE (FRENCH):           AGONISTES DU RECEPTEUR (VPAC2) DU TYPE PEPTIDES
                           ACTIVANT L'ADENYLATE CYCLASE HYPOPHYSIAIRE (PACAP) ET
                           PROCEDES PHARMACOLOGIQUES D'UTILISATION DE CES
                           AGONISTES

```

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Corporation, 400 Morgan Lane, West Haven, Connecticut  
06516\$, US

LANGUAGE OF FILING: English  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005072385	A2	20050811

# DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO  
CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR  
HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV  
MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO  
RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ  
VC VN YU ZA ZM ZW

RW (ARIPO): BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW  
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM  
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT  
LT LU MC NL PL PT RO SE SI SK TR  
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2005-US2609 A 20050127  
PRIORITY INFO.: US 2004-60/539,550 20040127  
US 2004-60/566,499 20040429

L42 ANSWER 2 OF 5 PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 2005016974 PCTFULL ED 20050302 EW 200508  
TITLE (ENGLISH): SIALIC ACID DERIVATIVES FOR PROTEIN DERIVATISATION AND  
CONJUGATION  
TITLE (FRENCH): DERIVE D'ACIDE SIALIQUE DESTINE A LA DERIVATISATION ET  
A LA CONJUGAISON PROTEINIQUE  
INVENTOR(S): JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303,  
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 LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;  
 GREGORIADIS, Gregory, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB], for US only;  
 HRECZUK-HRIST, Dale, Howard, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;  
 PAPAIOANNOU, Yiannis, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GR, GB], for US only  
 AGENT: GILL JENNINGS & EVERY\$, Broadgate House, 7 Eldon Street, London EC2M 7LH\$, GB  
 LANGUAGE OF FILING: English  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005016974	A1	20050224

DESIGNATED STATES

W:

AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

RW (ARIPO): BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW

RW (EAPO): AM AZ BY KG KZ MD RU TJ TM

RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR

RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2004-GB3511 A 20040812

PRIORITY INFO.: EP 2003-03254989.1 20030812

L42 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2005 Univentio on STN  
 ACCESSION NUMBER: 2005016973 PCTFULL ED 20050302 EW 200508  
 TITLE (ENGLISH): POLYSIALIC ACID DERIVATIVES  
 TITLE (FRENCH): DERIVES D'ACIDE POLYSIALIQUE  
 INVENTOR(S): HRECZUK-HIRST, Dale, Howard, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];  
 JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [IN, GB];  
 LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];  
 GREGORIADIS, Gregory, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB];  
 PAPAIOANNOU, Iannis, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H

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 9BB, GB [CA, GB], for US only;  
 PAPAIOANNOU, Iannis, Lipoxon Technologies Limited,  
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 9BB, GB [GR, GB], for US only  
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 Street, London EC2M 7LH\$, GB  
 LANGUAGE OF FILING: English  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2005016973	A1	20050224
DESIGNATED STATES			
W:	AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW		
RW (ARIPO):	BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW		
RW (EAPO):	AM AZ BY KG KZ MD RU TJ TM		
RW (EPO):	AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR		
RW (OAPI):	BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 2004-GB3488	A	20040812
PRIORITY INFO.:	EP 2003-03254988.3		20030812
	EP 2003-03255200.2		20030821

=> d ibib 4-5

L42 ANSWER 4 OF 5 PCTFULL COPYRIGHT 2005 Univentio on STN  
 ACCESSION NUMBER: 2004030617 PCTFULL ED 20040421 EW 200416  
 TITLE (ENGLISH): POLYMER CONJUGATES WITH DECREASED ANTIGENICITY,  
 METHODS OF PREPARATION AND USES THEREOF  
 TITLE (FRENCH): CONJUGUES DE POLYMERES AVEC ANTIGENICITE REDUITE,  
 PROCEDES DE PREPARATION ET UTILISATIONS DE CES  
 CONJUGUES  
 INVENTOR(S): MARTINEZ, Alexa, L., 1944 Jonathan Avenue, San Jose, CA  
 95125, US;  
 SHERMAN, Merry, R., 1114 Royal Lane, San Carlos, CA  
 94070, US;  
 SAIFER, Mark, G., P., 1114 Royal Lane, San Carlos, CA  
 94070, US;  
 WILLIAMS, L. David, 37709 Arlene Court, Fremont, CA  
 94536, US  
 PATENT ASSIGNEE(S): MOUNTAIN VIEW PHARMACEUTICALS, INC., 3475-S Edison Way,

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GOLDSTEIN, Jorge A.\$, Sterne, Kessler, Goldstein & Fox,  
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20005\$, US  
LANGUAGE OF FILING: English  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2004030617	A2	20040415
DESIGNATED STATES			
W:	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW		
RW (ARIPO):	GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW		
RW (EAPO):	AM AZ BY KG KZ MD RU TJ TM		
RW (EPO):	AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR		
RW (OAPI):	BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 2003-US29989	A	20030925
PRIORITY INFO.:	US 2002-60/414,424		20020930
	US 2002-10/317,092		20021212

L42 ANSWER 5 OF 5 PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 2001015726 PCTFULL ED 20020828  
TITLE (ENGLISH): COMPOSITIONS FOR STIMULATING CYTOKINE SECRETION AND  
INDUCING AN IMMUNE RESPONSE  
TITLE (FRENCH): COMPOSITIONS STIMULANT LA SECRETION DE CYTOKINE ET  
PROVOQUANT UNE REACTION IMMUNITAIRE  
INVENTOR(S): SEMPLE, Sean, C.;  
HARASYM, Troy, O.;  
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KOJIC, Ljiljiana, D.;  
BRAMSON, Jonathan, L.;  
MUI, Barbara;  
HOPE, Michael, J.  
PATENT ASSIGNEE(S): INEX PHARMACEUTICALS CORP.;  
SEMPLE, Sean, C.;  
HARASYM, Troy, O.;  
KLIMUK, Sandra, K.;  
KOJIC, Ljiljiana, D.;  
BRAMSON, Jonathan, L.;  
MUI, Barbara;  
HOPE, Michael, J.  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2001015726	A2	20010308
DESIGNATED STATES			
W:	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 2000-CA1013	A	20000828

PRIORITY INFO.:           US 1999-60/151,211           19990827  
                  US 2000-60/176,406           20000113

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005

E "PEG"/CN 25

L1           1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2           185 S L1  
L3           9685 S PEG  
L4           2487 S POLY ( ) ETHYLENE ( ) GLYCOL  
L5           52 S METHOXPOLY ( ) ETHYLENE GLYCOL  
L6           10866 S L5 OR L4 OR L3  
L7           694206 S ANTIBOD?  
L8           538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L9           1041 S L8 AND L6  
L10          129 S L9 AND L7  
L11          7 S ANTI-PEG  
L12          2 S L11 AND L8  
L13          3 S L11 NOT PY>1999  
L14          97 S L10 NOT PY>1999  
L15          90 S L14 NOT PY>1998  
L16          1898836 S INCREASE? OR ACCELERAT?  
L17          24 S L16 AND L15  
L18          51664 S L16 (S) L8  
L19          7 S L18 AND L17

FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005

L20          33476 S PEG  
L21          12996 S POLY ( ) ETHYLENE ( ) GLYCOL  
L22          144 S METHOXPOLY ( ) ETHYLENE GLYCOL  
L23          41717 S L22 OR L21 OR L20  
L24          440322 S ANTIBOD?  
L25          1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L26          1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L27          3736368 S INCREASE? OR ACCELERAT?  
L28          99738 S L26 (S) L27  
L29          1750 S L24 AND L28  
L30          16 S L29 AND L23  
L31          9 S ANTI-PEG  
L32          3 S L31 NOT PY>1999  
L33          6 S L30 NOT PY>1998

FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005

L34          35377 S PEG  
L35          5321 S POLY ( ) ETHYLENE ( ) GLYCOL  
L36          76 S METHOXPOLY ( ) ETHYLENE GLYCOL  
L37          80487 S ANTIBOD?  
L38          492783 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L39          496097 S INCREASE? OR ACCELERAT?  
L40          83462 S L38 (S) L39  
L41          7 S ANTI-PEG  
L42          5 S L41 AND L40

=> s 134 or 135 or 136

L43          38102 L34 OR L35 OR L36

=> s 143 (S) 137

L44 3934 L43 (S) L37

=> s 144 and 140

L45 1413 L44 AND L40

=> s 144 (P) 140

L46 1018 L44 (P) L40

=> s anti-(polyethylene glycol)

MISSING OPERATOR 'ANTI-(POLYETHYLE'

The search profile that was entered contains terms or nested terms that are not separated by a logical operator.

=> s anti () (polyethylene glycol)

159836 ANTI

158 ANTIS

159865 ANTI

(ANTI OR ANTIS)

123593 POLYETHYLENE

5298 POLYETHYLENES

124334 POLYETHYLENE

(POLYETHYLENE OR POLYETHYLENES)

99346 GLYCOL

38678 GLYCOLS

106001 GLYCOL

(GLYCOL OR GLYCOLS)

62856 POLYETHYLENE GLYCOL

(POLYETHYLENE(W)GLYCOL)

L47 3 ANTI (W) (POLYETHYLENE GLYCOL)

=> d ibib 1-3

L47 ANSWER 1 OF 3

ACCESSION NUMBER:

TITLE (ENGLISH):

TITLE (FRENCH):

INVENTOR(S):

PATENT ASSIGNEE(S):

PCTFULL COPYRIGHT 2005 Univentio on STN

2005016974 PCTFULL ED 20050302 EW 200508

SIALIC ACID DERIVATIVES FOR PROTEIN DERIVATISATION AND CONJUGATION

DERIVE D'ACIDE SIALIQUE DESTINE A LA DERIVATISATION ET A LA CONJUGAISON PROTEINIQUE

JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [IN, GB];

LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];

GREGORIADIS, Gregory, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB];

HRECZUK-HRIST, Dale, Howard, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];

PAPAOANNOU, Yiannis, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GR, GB]

LIPOXEN TECHNOLOGIES LIMITED, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for all designates States except US;

JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [IN, GB], for US only;

LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;

GREGORIADIS, Gregory, Lipoxen Technologies Limited,

Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB], for US only;  
HRECZUK-HRIST, Dale, Howard, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;  
PAPAOANNOU, Yiannis, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GR, GB], for US only  
GILL JENNINGS & EVERY\$, Broadgate House, 7 Eldon Street, London EC2M 7LH\$, GB

AGENT:

LANGUAGE OF FILING:

LANGUAGE OF PUBL.:

DOCUMENT TYPE:

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005016974	A1	20050224

DESIGNATED STATES

W:

AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO  
CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR  
HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV  
MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO  
RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ  
VC VN YU ZA ZM ZW

RW (ARIPO):

BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW

RW (EAPO):

AM AZ BY KG KZ MD RU TJ TM

RW (EPO):

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU  
MC NL PL PT RO SE SI SK TR

RW (OAPI):

BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.:

WO 2004-GB3511 A 20040812

PRIORITY INFO.:

EP 2003-03254989.1 20030812

L47 ANSWER 2 OF 3

PCTFULL COPYRIGHT 2005 Univentio on STN

ACCESSION NUMBER:

2005016973 PCTFULL ED 20050302 EW 200508

TITLE (ENGLISH):

POLYSIALIC ACID DERIVATIVES

TITLE (FRENCH):

DERIVES D'ACIDE POLYSIALIQUE

INVENTOR(S):

HRECZUK-HIRST, Dale, Howard, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];  
JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [IN, GB];  
LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];  
GREGORIADIS, Gregory, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB];  
PAPAIIOANNOU, Iaonnis, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GR, GB]  
PATENT ASSIGNEE(S):  
LIPOXEN TECHNOLOGIES LIMITED, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for all designates States except US;  
HRECZUK-HIRST, Dale, Howard, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;  
JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [IN, GB], for US only;  
LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;



GREGORIADIS, Gregory, Lipoxen Technologies Limited,  
Suite 303, Hamilton House, Mabledon Place, London WC1H  
9BB, GB [CA, GB], for US only;  
PAPAIOANNOU, Ioannis, Lipoxen Technologies Limited,  
Suite 303, Hamilton House, Mabledon Place, London WC1H  
9BB, GB [GR, GB], for US only

AGENT: GILL JENNINGS & EVERY\$, Broadgate House, 7 Eldon  
Street, London EC2M 7LH\$, GB

LANGUAGE OF FILING: English

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005016973	A1	20050224

DESIGNATED STATES

W:

AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO  
CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR  
HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV  
MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO  
RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ  
VC VN YU ZA ZM ZW

RW (ARIPO):

BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW

RW (EAPO):

AM AZ BY KG KZ MD RU TJ TM

RW (EPO):

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU  
MC NL PL PT RO SE SI SK TR

RW (OAPI):

BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.:

WO 2004-GB3488 A 20040812

PRIORITY INFO.:

EP 2003-03254988.3 20030812

EP 2003-03255200.2 20030821

L47 ANSWER 3 OF 3

ACCESSION NUMBER:

PCTFULL COPYRIGHT 2005 Univentio on STN

TITLE (ENGLISH):

2004022000 PCTFULL ED 20040324 EW 200412  
ANTIBIOTIC MICROSPHERES FOR TREATMENT OF INFECTIONS AND  
OSTEOMYELITIS

TITLE (FRENCH):

MICROSPHERES ANTIBIOTIQUES POUR LE TRAITEMENT  
D'INFECTIONS ET DE L'OSTEOMYELITE

INVENTOR(S):

AMBROSE, Catherine, G., 6431 Fannin, Houston, TX 77030,  
US [US, US];

CLYBURN, Terry, A, 6431 Fannin, Houston, TX 77030, US  
[US, US];

MIKOS, Antonios, G., P.O. Box 1892, Houston, TX 77251,  
US [US, US]

PATENT ASSIGNEE(S):

AMBROSE, Catherine, G., 6431 Fannin, Houston, TX 77030,  
US [US, US];

CLYBURN, Terry, A, 6431 Fannin, Houston, TX 77030, US  
[US, US];

MIKOS, Antonios, G., P.O. Box 1892, Houston, TX 77251,  
US [US, US]

AGENT:

RODDY, Kenneth, A.\$, Suite 100, 2916 West T.C. Jester,  
Houston, TX 77018\$, US

LANGUAGE OF FILING: English

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004022000	A2	20040318

DESIGNATED STATES

W:

AE AG AL AU BA BB BR BZ CA CN CO CR CU DM DZ EC GD GE  
HR ID IL IN IS JP KP KR LC LK LR LT LV MA MG MK MN MX  
NI NO NZ OM PG PH PL SC SG SY TN TT UA UZ VC VN YU ZA  
GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

RW (ARIPO):

RW (EAPO):	AM AZ BY KG KZ MD RU TJ TM
RW (EPO):	AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU
	MC NL PT RO SE SI SK TR
RW (OAPI):	BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.:	WO 2003-US28010 A 20030905
PRIORITY INFO.:	US 2002-60/408,496 20020905
	US 2002-60/408,502 20020905

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005

E "PEG"/CN 25

L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2 185 S L1  
L3 9685 S PEG  
L4 2487 S POLY ( ) ETHYLENE ( ) GLYCOL  
L5 52 S METHOXPOLY ( ) ETHYLENE GLYCOL  
L6 10866 S L5 OR L4 OR L3  
L7 694206 S ANTIBOD?  
L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L9 1041 S L8 AND L6  
L10 129 S L9 AND L7  
L11 7 S ANTI-PEG  
L12 2 S L11 AND L8  
L13 3 S L11 NOT PY>1999  
L14 97 S L10 NOT PY>1999  
L15 90 S L14 NOT PY>1998  
L16 1898836 S INCREASE? OR ACCELERAT?  
L17 24 S L16 AND L15  
L18 51664 S L16 (S) L8  
L19 7 S L18 AND L17

FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005

L20 33476 S PEG  
L21 12996 S POLY ( ) ETHYLENE ( ) GLYCOL  
L22 144 S METHOXPOLY ( ) ETHYLENE GLYCOL  
L23 41717 S L22 OR L21 OR L20  
L24 440322 S ANTIBOD?  
L25 1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L26 1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L27 3736368 S INCREASE? OR ACCELERAT?  
L28 99738 S L26 (S) L27  
L29 1750 S L24 AND L28  
L30 16 S L29 AND L23  
L31 9 S ANTI-PEG  
L32 3 S L31 NOT PY>1999  
L33 6 S L30 NOT PY>1998

FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005

L34 35377 S PEG  
L35 5321 S POLY ( ) ETHYLENE ( ) GLYCOL  
L36 76 S METHOXPOLY ( ) ETHYLENE GLYCOL  
L37 80487 S ANTIBOD?  
L38 492783 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L39 496097 S INCREASE? OR ACCELERAT?  
L40 83462 S L38 (S) L39  
L41 7 S ANTI-PEG  
L42 5 S L41 AND L40

L43 38102 S L34 OR L35 OR L36  
 L44 3934 S L43 (S) L37  
 L45 1413 S L44 AND L40  
 L46 1018 S L44 (P) L40  
 L47 3 S ANTI ( ) (POLYETHYLENE GLYCOL)

=> s 146 not py>1999  
 581472 PY>1999  
 L48 282 L46 NOT PY>1999

=> s 143/ab  
 662 PEG/AB  
 227 PEGS/AB  
 831 PEG/AB  
 ((PEG OR PEGS)/AB)  
 3882 POLY/AB  
 132 POLIES/AB  
 4014 POLY/AB  
 ((POLY OR POLIES)/AB)  
 6371 ETHYLENE/AB  
 22 ETHYLENES/AB  
 6377 ETHYLENE/AB  
 ((ETHYLENE OR ETHYLENES)/AB)  
 3431 GLYCOL/AB  
 453 GLYCOLS/AB  
 3707 GLYCOL/AB  
 ((GLYCOL OR GLYCOLS)/AB)  
 122 POLY/AB (W) ETHYLENE/AB (W) GLYCOL/AB  
 0 METHOXYPOLY/AB  
 6371 ETHYLENE/AB  
 22 ETHYLENES/AB  
 6377 ETHYLENE/AB  
 ((ETHYLENE OR ETHYLENES)/AB)  
 3431 GLYCOL/AB  
 453 GLYCOLS/AB  
 3707 GLYCOL/AB  
 ((GLYCOL OR GLYCOLS)/AB)  
 604 ETHYLENE GLYCOL/AB  
 ((ETHYLENE(W) GLYCOL)/AB)  
 0 METHOXYPOLY/AB (W) ETHYLENE GLYCOL/AB  
 L49 930 ((PEG/AB) OR (POLY/AB (W) ETHYLENE/AB (W) GLYCOL/AB) OR (METHOXY  
 POLY/AB (W) ETHYLENE GLYCOL/AB))

=> s 149 and 148  
 L50 12 L49 AND L48

=> s 150 not py>1998  
 649032 PY>1998  
 L51 11 L50 NOT PY>1998

=> d ibib 1-5

L51	ANSWER 1 OF 11	PCTFULL	COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:		1998048837	PCTFULL ED 20020514
TITLE (ENGLISH):		POLYALKYLENE OXIDE-MODIFIED SINGLE CHAIN POLYPEPTIDES	
TITLE (FRENCH):		POLYPEPTIDES A CHAINE UNIQUE MODIFIES PAR OXYDE DE	
		POLYALKYLENE	
INVENTOR(S):		WHITLOW, Marc;	
		SHORR, Robert, G., L.;	
		FILPULA, David, R.;	
		LEE, Lihsyng, S.	
PATENT ASSIGNEE(S):		ENZON, INC.	
LANGUAGE OF PUBL.:		English	

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
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WO 9848837	A1	19981105
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DESIGNATED STATES

W:

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE  
ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC  
LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU  
SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM  
KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE  
CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ  
CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.:

WO 1998-US8654	A	19980430
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PRIORITY INFO.:

US 1997-60/044,449		19970430
US 1997-60/050,472		19970623
US 1997-60/063,074		19971027
US 1997-60/067,341		19971202

L51 ANSWER 2 OF 11

PCTFULL COPYRIGHT 2005 Univentio on STN

ACCESSION NUMBER:

1998044143 PCTFULL ED 20020514

TITLE (ENGLISH):

POLYMER-MODIFIED VIRUSES

TITLE (FRENCH):

VIRUS MODIFIES PAR DES POLYMERES

INVENTOR(S):

SMITH, Alan, E.;  
O'RIORDAN, Catherine, R.;  
FRANCIS, Gillian, E.;  
PARKES, Vincent;  
DELGADO, Christina

PATENT ASSIGNEE(S):

GENZYME CORPORATION;  
POLYMASC PHARMACEUTICAL, PLC;  
SMITH, Alan, E.;  
O'RIORDAN, Catherine, R.;  
FRANCIS, Gillian, E.;  
PARKES, Vincent;  
DELGADO, Christina

LANGUAGE OF PUBL.:

English

DOCUMENT TYPE:

Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
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WO 9844143	A1	19981008
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DESIGNATED STATES

W:

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE  
ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC  
LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU  
SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH  
GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT  
BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF  
BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.:

WO 1998-US6609	A	19980403
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PRIORITY INFO.:

GB 1997-9706735.9		19970403
GB 1997-9719625.7		19970915
GB 1997-9722316.8		19971022

L51 ANSWER 3 OF 11

PCTFULL COPYRIGHT 2005 Univentio on STN

ACCESSION NUMBER:

1997010847 PCTFULL ED 20020514

TITLE (ENGLISH):

TARGETING OF CONJUGATES OF POLY(ETHYLENE GLYCOL) AND  
ANTIBODIES AGAINST GLUTAMIC ACID DECARBOXYLASE TO ISLET  
CELLS

TITLE (FRENCH):

CIBLAGE DE CONJUGUES DE POLY(ETHYLENE GLYCOL) ET  
D'ANTICORPS CONTRE L'ACIDE GLUTAMIQUE DECARBOXYLASE SUR  
DES CELLULES INSULAIRES

INVENTOR(S):

JACOBS, Harvey;

PATENT ASSIGNEE(S): KIM, Sung, Wan;  
 LANGUAGE OF PUBL.: MENARD, Virginie  
 DOCUMENT TYPE: UNIVERSITY OF UTAH RESEARCH FOUNDATION  
 PATENT INFORMATION: English  
 Patent

NUMBER	KIND	DATE
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WO 9710847	A1	19970327
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DESIGNATED STATES

W:

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE  
 ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT  
 LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI  
 SK TJ TM TR TT UA UG UZ VN KE LS MW SD SZ UG AM AZ BY  
 KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT  
 LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD  
 TG

APPLICATION INFO.: WO 1996-US15219 A 19960920  
 PRIORITY INFO.: US 1995-60/004,109 19950921

L51 ANSWER 4 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
 ACCESSION NUMBER: 1997003092 PCTFULL ED 20020514  
 TITLE (ENGLISH): A PROCESS FOR REMOVAL OF POLYETHYLENE GLYCOL FROM A  
 PROTEIN OR PEPTIDE SOLUTION  
 TITLE (FRENCH): PROCEDE POUR ELIMINER LE POLYETHYLENEGLYCOL D'UNE  
 SOLUTION DE PROTEINES OU DE PEPTIDES

INVENTOR(S): KAERSGAARD, Per;  
 CARLSEN, Soren, Knud

PATENT ASSIGNEE(S): HEMASURE A/S;  
 KAERSGAARD, Per;  
 CARLSEN, Soren, Knud

LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
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WO 9703092	A1	19970130
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DESIGNATED STATES

W:

JP US AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 1996-DK314 A 19960710  
 PRIORITY INFO.: DK 1995-823/95 19950713  
 DK 1995-970/95 19950904

L51 ANSWER 5 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
 ACCESSION NUMBER: 1996034015 PCTFULL ED 20020514  
 TITLE (ENGLISH): MODIFIED ANTI-ICAM-1 ANTIBODIES AND THEIR USE IN THE  
 TREATMENT OF INFLAMMATION  
 TITLE (FRENCH): ANTICORPS ANTI-ICAM-1 MODIFIES ET LEUR UTILISATION DANS  
 LE TRAITEMENT DES INFLAMMATIONS

INVENTOR(S): FAANES, Ronald, B.;  
 MC GOFF, Paul, E.;  
 SHIRLEY, Bret, A.;  
 SCHER, David, S.

PATENT ASSIGNEE(S): BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.;  
 FAANES, Ronald, B.;  
 MC GOFF, Paul, E.;  
 SHIRLEY, Bret, A.;  
 SCHER, David, S.

LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
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	-----	
	WO 9634015	A1 19961031
DESIGNATED STATES		
W:	AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG	
APPLICATION INFO.:	WO 1996-US5550	A 19960423
PRIORITY INFO.:	US 1995-8/427,355	19950424

=> d kwic 4

L51 ANSWER 4 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN

ABEN Polyethylene is used for fractional precipitation of proteins and peptides. Protein and peptide fractions obtained by the **PEG** fractionation methods generally contains residual **PEG**. The invention relates to a process for removing contaminating **PEG** from a solution of proteins or peptides, which process comprises adsorption of **PEG** in the protein or peptide solution to activated carbon.

ABFR . . . fractionnaire des proteines et des peptides. Les fractions de proteines et de peptides obtenues selon les methodes de fractionnement par **PEG** contiennent generalement des residus de **PEG**. La presente invention concerne un procede permettant d'eliminer d'une solution de proteines ou de peptides le **PEG** contaminant, lequel procede consiste a adsorber le **PEG** contenu dans la solution sur un carbone active.

DETD . . . application having publication number 123,375 describes manufacturing of a dry y-globulin preparation capable of intravenous injection by fractionating human plasma 5 with **PEG**. The method provides a y-globulin preparation with improved water solubility and stability against increase of anticomplementary activity and decrease of **antibody** titer.

In one aspect of this invention, the activated carbon is added to the **PEG**-containing protein or peptide solution batchwise, and after. . . **PEG**, the activated carbon is separated from the solution by methods known per se such as centrifugation, sedimentation, or filtration. The **removed** activated carbon may subsequently be washed and the washing solution may be added to the purified, more protein or peptide containing solution, to **increase** the recovery of, for example, a valuable protein or peptide in the purified solution.

. . . carbon filter with a flow rate that permits the adsorption of the **PEG** to the activated carbon in the filter. The **removal** of the **PEG** by filtration may be 10 combined with the **removal** of other contaminating substances, with a decolorization, or with a clarification of the solution by the activated carbon filter. The filtration. . . may subsequently be washed and the washing solution may be added to the purified more protein or peptide containing

solution, to  
15 **increase** the recovery of e.g. a valuable protein or peptide  
in the treated solution.

=> d kwic 3

L51 ANSWER 3 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ABEN . . . coupled to a nonimmunogenic hydrophilic polymer that provides a  
hydration  
shell around the monoclonal antibody for inhibiting immune recognition  
thereof. **Poly(ethylene glycol)** is a preferred polymer. A method of reducing insulinitis  
in an IDDM patient and a composition  
therefor are also described.

ABFR . . . non immunogene  
qui forme une enveloppe d'hydratation autour de l'anticorps monoclonal  
en vue d'inhiber la  
reconnaissance immune de celui-ci. Le **poly(ethylene glycol)** est un polymere prefere. L'invention se  
rapporte egalement a un procede de reduction de l'insulite chez un  
patient atteint d'IDDM, . . .

DETD TARGETING OF CONJUGATES OF **POLY(ETHYLENE GLYCOL)** AND **ANTIBODIES** AGAINST  
GLUTAMIC ACID DECARBOXYLASE TO ISLET CELLS 11  
CROSS-REFERENCE TO RELATED APPLICATIONS  
This application claims the benefit of U.S.

From an immunotherapeutic approach, overt early  
stage diabetes has been treated by blocking the  
activating receptors on T cells with monoclonal  
**antibodies**. In one such study, anti-lymphocyte serum  
(ALS) and **antibodies** directed against CD4 and Cd8 T cell  
receptors were administered to diabetic mice. T. Maki  
et al., Long-term Abrogation of Autoimmune Diabetes. . . within 30  
days after  
treatment and lasted for about 200 days. Several  
significant points about the autoimmunity of diabetes  
were observed. The lymphocytic **antibodies** were  
responsible for termination of the immune response,  
thereby allowing islet recovery. Also, if **antibody**  
BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS  
FIG. 1 shows the reactions for coupling methoxy-  
**PEG**-amine to an F(abl) fragment with a  
heterobifunctional crosslinker.

Preferably, the polymer is a **poly (ethylene glycol)** ,  
and more preferably has a molecular weight in the range  
of about 200 to 8,000, although higher molecular weight  
polymers, branched polymers, star molecules, and **PEG**  
block copolymers are also within the scope of the  
invention. Methoxy-**PEG** is a particularly preferred  
polymer. It is also preferred that the monoclonal  
**antibody** or fragment thereof is an F (ab I ) fragment.

In the present invention, anti-GAD monoclonal  
**antibodies** (Mab) are modified to maintain binding to  
their cognate antigens while further preventing  
recognition by other aspects of the immune system. In  
an illustrative embodiment, the anti-GAD **antibody** is  
modified by digestion with a protease and chemical

reduction with a reducing agent to yield F(ab') fragments, which are then conjugated with various poly(ethylene glycol) polymers (PEG). The F(ab') fragment retains the antigen-specific Fab binding fragment, while the immune and complement activating Fc fragment is removed. In addition, the poly(ethylene glycol) moiety provides an increased hydration sphere and dynamic mobility that prevents protein and cellular interaction. Thus, the present anti-GAD-F(ab')-PEG composition simultaneously binds GAD and prevents or inhibits further recognition by the immune system.

**Antibodies** administered to experimental animals and hydrophilic surfaces, due to the hydrating effect of PEG. More importantly, protein (albumin and other plasma proteins) adsorption was greatly reduced, resulting from the high chain motility, hydration sphere, and protein exclusion properties of PEG.

pH 7.3) and then incubated in 250  $\mu$ l of blocking buffer for 1 hour at 37°C. After incubation, the blocking buffer was removed and the Immunol. 98-104 (1978), hereby incorporated by reference. To further increase the immune reactivity of the F(ab') fragment, poly(ethylene glycol) (PEG) is conjugated to the F(ab') molecule. PEG is a linear or branched, neutral.

ascites fluid was microplate was dried. Duplicate dilutions (50  $\mu$ l) of samples containing anti-GAD (IgG, F(ab'), or F(ab')-PEG) (serum or dilutions of chromatographic fractions) were placed in the wells and incubated for 2 hours at 37°C, followed by 3 washes with. . . microplate autoreader (EL311, is Bio-Tek Instruments). These values were compared to standard curves prepared with known anti-GAD concentrations to extrapolate the anti-GAD antibody concentration.

either Example 1 or Example 2 was enzymatically digested and then chemically reduced to obtain F(ab') fragments, which could then be coupled to PEG. The rationale behind this procedure is to obtain an antibody fragment capable of binding to the GAD antigen yet which lacks the Fc domain, and is conjugated with PEG to further decrease protein and cellular interactions.

It was anticipated that the antibodies isolated during the previous procedures were a mixture of anti-GAD and indigenous mouse antibodies. As a final antigenicity of foreign immunogenic proteins and enzymes. Therefore, PEGs of various molecular weights are coupled to the F(ab') fragments through the sulfhydryl groups thereof. These anti-GAD-F(ab')-PEG compositions maintain ability to bind to islet/beta cells while the PEG moiety masks the remainder of the F(ab') molecule from eliciting additional immunological events.



#### Example 8

Coupling of Anti-GAD-F(abl) to Activated **PEG**

In this example, a **PEG** intermediate prepared according to the procedure of Examples 4, 6, or 7 is

#### Example 5

Activation of Diamino-**PEG**

For cell staining and whole body perfusion

(pharmacokinetic) evaluations, it is useful to label anti-GAD-F(abl)-**PEG** with, for example, a radioactive or fluorescent label. In vivo therapeutic applications of the anti-GAD-F(abl)-**PEG** generally do not require such labels. Current methods of labeling **antibodies** involve forming conjugates through amine groups (fluorescent or <sup>125</sup>I labels) or through oxidation of tyrosine residues (<sup>125</sup>I, label) These labeling methods can interfere with **antibody** binding through reaction with the active site of the **antibody**. Therefore, this example shows coupling of the label to the **PEG** moiety. The labeled **PEG** moiety

is later coupled to the F (ab I ) fragment. This procedure assures that labeled and unlabeled compositions have similar affinities for. . .

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005

E "PEG"/CN 25

L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2 185 S L1  
L3 9685 S PEG  
L4 2487 S POLY ( ) ETHYLENE ( ) GLYCOL  
L5 52 S METHOXPOLY ( ) ETHYLENE GLYCOL  
L6 10866 S L5 OR L4 OR L3  
L7 694206 S ANTIBOD?  
L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L9 1041 S L8 AND L6  
L10 129 S L9 AND L7  
L11 7 S ANTI-PEG  
L12 2 S L11 AND L8  
L13 3 S L11 NOT PY>1999  
L14 97 S L10 NOT PY>1999  
L15 90 S L14 NOT PY>1998  
L16 1898836 S INCREASE? OR ACCELERAT?  
L17 24 S L16 AND L15  
L18 51664 S L16 (S) L8  
L19 7 S L18 AND L17

FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005

L20 33476 S PEG  
L21 12996 S POLY ( ) ETHYLENE ( ) GLYCOL  
L22 144 S METHOXPOLY ( ) ETHYLENE GLYCOL  
L23 41717 S L22 OR L21 OR L20  
L24 440322 S ANTIBOD?  
L25 1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L26 1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L27 3736368 S INCREASE? OR ACCELERAT?  
L28 99738 S L26 (S) L27  
L29 1750 S L24 AND L28

L30 16 S L29 AND L23  
L31 9 S ANTI-PEG  
L32 3 S L31 NOT PY>1999  
L33 6 S L30 NOT PY>1998

FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005

L34 35377 S PEG  
L35 5321 S POLY ( ) ETHYLENE ( ) GLYCOL  
L36 76 S METHOXPOLY ( ) ETHYLENE GLYCOL  
L37 80487 S ANTIBOD?  
L38 492783 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
L39 496097 S INCREASE? OR ACCELERAT?  
L40 83462 S L38 (S) L39  
L41 7 S ANTI-PEG  
L42 5 S L41 AND L40  
L43 38102 S L34 OR L35 OR L36  
L44 3934 S L43 (S) L37  
L45 1413 S L44 AND L40  
L46 1018 S L44 (P) L40  
L47 3 S ANTI ( ) (POLYETHYLENE GLYCOL)  
L48 282 S L46 NOT PY>1999  
L49 930 S L43/AB  
L50 12 S L49 AND L48  
L51 11 S L50 NOT PY>1998

=> d ibib 6-10

L51 ANSWER 6 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 1994029370 PCTFULL ED 20020513  
TITLE (ENGLISH): FACTOR IX - POLYMERIC CONJUGATES  
TITLE (FRENCH): CONJUGUES POLYMERES MODIFIANT L'ACTIVITE DU FACTEUR IX  
INVENTOR(S): HALLAHAN, Terrence, W.;  
GILBERT, Carl, W.  
PATENT ASSIGNEE(S): ENZON, INC.  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
-----		
WO 9429370	A1	19941222

DESIGNATED STATES

W:

AU BG BR CA CZ FI HU JP KP KR LK MG MN MW NO NZ PL PT  
RO RU SE SK UA AT BE CH DE DK ES FR GB GR IE IT LU MC  
NL PT SE

APPLICATION INFO.: WO 1994-US6388 A 19940607  
PRIORITY INFO.: US 1993-8/073,531 19930608

L51 ANSWER 7 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ACCESSION NUMBER: 1994022429 PCTFULL ED 20020513  
TITLE (ENGLISH): SOLID-TUMOR TREATMENT METHOD  
TITLE (FRENCH): PROCEDE DE TRAITEMENT D'UNE TUMEUR SOLIDE  
INVENTOR(S): ALLEN, Theresa, M.;  
MARTIN, Francis, J.;  
WOODLE, Martin, C.;  
ZALIPSKY, Samuel  
PATENT ASSIGNEE(S): LIPOSOME TECHNOLOGY, INC.;  
ALLEN, Theresa, M.;  
MARTIN, Francis, J.;  
WOODLE, Martin, C.;  
ZALIPSKY, Samuel

LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

	NUMBER	KIND	DATE
	-----		
	WO 9422429	A1	19941013
DESIGNATED STATES			
W:	AU CA JP US AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	WO 1994-US3457	A	19940330
PRIORITY INFO.:	US 1993-8/040,544		19930331
L51 ANSWER 8 OF 11	PCTFULL COPYRIGHT 2005 Univentio on STN		
ACCESSION NUMBER:	1994015625 PCTFULL ED 20020513		
TITLE (ENGLISH):	FACTOR VIII - POLYMERIC CONJUGATES		
TITLE (FRENCH):	CONJUGUES DE POLYMERES ET DE FACTEUR VIII		
INVENTOR(S):	HALLAHAN, Terrence, W.; GILBERT, Carl, W.		
PATENT ASSIGNEE(S):	ENZON, INC.		
LANGUAGE OF PUBL.:	English		
DOCUMENT TYPE:	Patent		
PATENT INFORMATION:			
	NUMBER	KIND	DATE
	-----		
	WO 9415625	A1	19940721
DESIGNATED STATES			
W:	AU BG BR CA CZ FI HU JP KP KR LK MG MN MW NO NZ PL PT RO RU SE SK UA AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	WO 1994-US552	A	19940113
PRIORITY INFO.:	US 1993-8/003,985		19930115
L51 ANSWER 9 OF 11	PCTFULL COPYRIGHT 2005 Univentio on STN		
ACCESSION NUMBER:	1993000109 PCTFULL ED 20020513		
TITLE (ENGLISH):	METHOD OF STIMULATING IMMUNE RESPONSE USING GROWTH HORMONE		
TITLE (FRENCH):	PROCEDE DE STIMULATION DE LA REPOSE IMMUNITAIRE A L'AIDE D'HORMONE DE CROISSANCE		
INVENTOR(S):	CARLSSON, Lena, Mariana, Susann; CLARK, Ross, G.; CRONIN, Michael, J.; JARDIEU, Paula, M.		
PATENT ASSIGNEE(S):	GENENTECH, INC.		
LANGUAGE OF PUBL.:	English		
DOCUMENT TYPE:	Patent		
PATENT INFORMATION:			
	NUMBER	KIND	DATE
	-----		
	WO 9300109	A1	19930107
DESIGNATED STATES			
W:	AU CA JP AT BE CH DE DK ES FR GB GR IT LU MC NL SE		
APPLICATION INFO.:	WO 1992-US4489	A	19920529
PRIORITY INFO.:	US 1991-723,359		19910628
L51 ANSWER 10 OF 11	PCTFULL COPYRIGHT 2005 Univentio on STN		
ACCESSION NUMBER:	1990004606 PCTFULL ED 20020513		
TITLE (ENGLISH):	A PROCESS FOR FRACTIONATING POLYETHYLENE GLYCOL (PEG)-PROTEIN ADDUCTS AND AN ADDUCT OF PEG AND GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR		
TITLE (FRENCH):	PROCEDE DE FRACTIONNEMENT DE PRODUITS D'ADDITION DE PROTEINE-POLYETHYLENE GLYCOL (PEG) AINSI QU'UN PRODUIT D'ADDITION DE PEG ET UNFACTEUR DE STIMULATION DE COLONIES DE GRANULOCYTES-MACROPHAGES		
INVENTOR(S):	FISHER, Derek; FRANCIS, Gillian, Elizabeth; DELGADO, Cristina		

PATENT ASSIGNEE(S): ROYAL FREE HOSPITAL SCHOOL OF MEDICINE;  
 FISHER, Derek;  
 FRANCIS, Gillian, Elizabeth;  
 DELGADO, Cristina  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO. 9004606	A1	19900503
DESIGNATED STATES			
W:	AT BE CH DE FR GB IT JP LU NL SE US		
APPLICATION INFO.:	WO 1989-GB1261	A	19891020
PRIORITY INFO.:	GB 1988-8824591.5		19881020

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L51 ANSWER 7 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
 ABEN . . . composition has sizes predominantly in the range 0.05 to 0.12  
 microns,  
 includes doxorubicin in entrapped form, and contains, on the **PEG**  
 free ends, a monoclonal antibody  
 specific against highly proliferative cells in a lung squamous cell  
 carcinoma.

ABFR . . . fois le temps de  
 circulation dans le sang desdits liposomes par rapport a celui de  
 liposomes depourvus de cette  
 couche **PEG**. Des anticorps ou fragments d'anticorps (16),  
 efficaces pour se lier specifiquement aux  
 antigenes associes a la tumeur, presents sur le. . .  
 entre 0,05 et 0,12 microns, renferme de la doxorubicine sous forme  
 piegee, et contient, sur les  
 extremités libres des chaines **PEG**, un anticorps monoclonal  
 specifiquement dirige contre des cellules  
 fortement proliferatives d'un epithelioma epidermoide bronchique.

DETD . . . accompanying figures and  
 examples,  
 Brief Description of the Figures  
 Fig\* 1 illustrates a portion of a liposome in  
 the liposome ocomposition of the invention, having  
**antibodies** or **antibody** fragments attached to the  
 free ends of polyethylene glycol (**PEG**) chains  
 carried on the liposome;  
 Fig 2 shows steps in forming a PE  
 derivatized by a **PEG** spacer chain having a  
 maleimide group at its free end;  
 Fig 3 illustrates the preparation of a  
 biotinylated PE-**PEG** for use in preparing liposomes  
 with **PEG**-bound biotin;  
 Fig. 4 shows coupling of an **antibody** to PE  
 derivatized with a **PEG** chain having a hydrazide  
 moiety at its free end;  
 Fig, 5 shows the coupling of an **antibody** to  
 PE derivatized by a **PEG** chain having a reactive  
 maleimide group at its free end;  
 Fig\* 6 shows the coupling of an **antibody** to a  
 liposome-attached **PEG** having a hydrazide group at  
 its free end;  
 Fig\* 7 is a plot of drug residence time in  
 the blood, expressed in terms of percent injected  
 dose, as a function of hours after IV injection in

rats, for liposomes containing  $^{67}\text{Ga}$  and a bound **antibody** IgG (9) or liposomes with no bound **antibody** (A);

Fig. 8 shows  $^{125}\text{I}$  uptake in normal and tumor-bearing DBA/2 mice (3/group) 45 days after i.v. injection of  $2 \times 10^5$ .

This embodiment allows the **antibody** in the polymer layer to be positioned at a selected depth in the layer to increase or decrease the extent to which the **antibody** is buried in the polymer layer. For example, if the **antibody** is a xenogeneic **antibody** which elicits an immunogenic response the **antibody** is preferably buried to hide immunogenic sites while retaining the antigen recognition region accessible for binding to a target site. If the **antibody** is nonimmunogenic, the **antibody** can be localized on the outer surface coating of polyethylene glycol chains. Functionalization of PEG chains for this purpose, referred to herein as a spacer chain, for attachment of an **antibody** is described below.

In another embodiment the **antibody** is a biotinylated **antibody** attached to the distal ends of liposome-attached polymer ends via a biotin-streptavidin (or biotin-avidin) linkage. In one embodiment, shown in Fig. 3, a DSPE-PEG-NH<sub>2</sub> is converted to DSPE-PEG-biotin. To the biotin moiety on the PEG free ends are bound avidin or streptavidin molecules. Each avidin molecule contains four high-affinity biotin binding sites and to one or more of these sites is attached the liposome bound biotin. To one or more of the free-remaining sites can be bound a biotinylated **antibody** which is derivatized by a biotin molecule.

The liposomes are then incubated with avidin and biotinylated **antibody**. Alternatively, a DSPE derivatized with a PEG chain having a hydrazide group at the chain's free end may be synthesized, as illustrated in Fig. 4\*. Here, a hydroxy acid derivative (IX) is prepared from PEG using ethyl isocyanatoacetate for partial introduction of a urethane-linked glycine residue.

30-75 percent vesicle-forming lipids, 25-40 percent cholesterol, 1-20 percent polymer-derivatized lipid, and 0-10 mole percent of the lipid derivative employed for **antibody** coupling, one exemplary liposome formulation includes hydrogenated soy phosphatidylethanolamine (HSPE), cholesterol (CH), DSPE-PEG at a molar ratio of 2:1:0.1. The composition also includes 0.05 mole percent phosphatidylethanolamine derivatized with biotin (biotin-PE). Another exemplary liposome formulation includes hydrogenated soy phosphatidylethanolamine (HSPE), cholesterol (CH), and DSPE-PEG at a molar ratio of 2:1:0. The composition also includes 1 mole percent DSPE-PEG derivatized with hydrazide (DSPE-PEG-Hz).

Alternatively, an **antibody**-lipid derivative may be first formed and then incorporated into a liposome. As an example, an **antibody** is coupled to the maleimide group of a free DSPE-PEG molecule. The **antibody**-coupled DSPE-PEG molecule is then employed to form vesicles.

Alternatively, the polymer end-functionalized group is a hydrazide group (see Figure 4 discussed above). Conveniently, the hydrazide can be coupled to the **antibody** through the carbohydrate moieties present in the **antibody**, as detailed in Figure 6 and Example 1.VIII. Briefly, **antibody** hydroxyl groups are oxidized to aldehydes by mild periodate oxidation. The oxidized protein is then added to liposomes containing DSPE-PEG-Hz and incubated overnight. Unbound **antibodies** are then separated from **antibody**-liposomes by gel filtration.

#### Ive Utility

According to an important aspect of the invention, it has been found that **antibodies** can be attached to the PEG chain free ends without a significant loss in the blood circulation lifetime of the liposomes. This allows the **antibody**-coated liposomes to circulate for the time necessary to reach remote tumor sites and to localize at the sites through **antibody**-antigen specific interactions. As a result, a significant therapeutic enhancement in tumor treatment over long-circulating liposomes in the absence of surface attached **antibodies** is possible.

#### A, Therapeutic Efficacy of **Antibody**-liposome Composition in vivo

Experiments were performed to investigate the half-life in the bloodstream and the tissue biodistribution of the **antibody** liposome composition. For these experiments liposomes containing PEG end-functionalized with a hydrazide group covalently linked to sheep IgG were prepared as described in Example 1.VIII.

The tissue biodistribution of liposomes containing <sup>125</sup>I-tyraminylinulin with and without covalently attached IgG **antibodies** is shown in Table I (Example 2(I)). It can be seen that the tissue biodistribution of liposomes containing **antibody** covalently attached to the end of a PEG chain by a hydrazide group is very similar to those of liposomes containing nonfunctionalized PEG chains. Liposome biodistribution was determined for the blood, liver, spleen, lung,, heart and carcass.

Other experiments to determine the blood circulation times of **antibody**-liposomes were performed using liposomes containing surface-bound avidin and biotinylated **antibodies**. Liposomes with surface-bound **antibodies** possessed long circulation times in the bloodstream similar to that of liposomes containing PEG derivatized

lipids but lacking the surface-bound **antibodies**.

Twenty-four hours post-injection  $34.7 \pm 6.7\%$  of  
.WO 94/22429 PCTIUS94/03457

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mAb liposomes were in the blood. This level is comparable to that of liposomes containing **PEG**, but lacking the **antibody** ( $37.5 \pm 9.7\%$  at 24 hours).

The results obtained indicate that liposomes containing entrapped doxorubicin, lipids derivatized with **PEG**, such as **PEG**DSPE, and containing an **antibody** on the liposomes' outer surface (mAb-liposomal DOX) are valuable for increasing the therapeutic effectiveness of doxorubicin administration to a site in a subject.

compound,  
multivalent species capable of binding multiple antibodies may be administered between about 24 to 48 hours after administration of the biotinylated antibodies to **accelerate clearance** of the antibodies from the bloodstream. These multivalent species may be empty liposomes having surface-bound avidin, but not containing the liposome-entrapped compound, The empty. . .

These multivalent species serve to chase nonspecifically-bound biotinylated **antibodies** from sites in the bloodstream. After the chase, liposomes containing the therapeutic compound in liposome-entrapped form, the surface-bound anti-ligand molecules, such as, avidin, and the **PEG** layer on the liposome surface are administered.

#### Example 1

Preparation of DSPE-**PEG**-Maleimide and **Antibody**

Coupling to DSPE-**PEG**-Maleimide

Io PreRaration of the Mono 2-nitrobenzene-sulfonamide of **PEG** bis(amine) (Compound II)

A mixture of 1.7 g (0.5 mmole) of commercially available polyethylene glycol bis(amine) and 104 mg (0.55 mmole) of 2-nitrobenzene. . .

#### VII. **Antibody** Coupling to the Maleimide Grou'P of **PEG**

Coupling reactions were performed by adding **antibody** solution to the liposomes (final protein concentration = 0.5 mg/ml) in phosphate buffered saline and incubating the suspension overnight at ambient temperature with. . .

#### VIII Io **Antibody** Coupling to the Hydrazide Group of **PEG**

A 10 mg/ml solution of IgG was prepared in 100 mM sodium acetate, 70 mM NaCl pH 5 For 1 ml of protein. . . of 0.2 M sodium periodate was added. oxidation proceeded- for 1 hour at room temperature. The periodate-treated protein was added to liposomes containing DSPE-**PEG** hydrazide and incubated overnight at 40C.

Liposomes were separated from free protein by chromatography on Sepharose CL-4B in TES-buffered saline, pH 7.4\*

#### Example 2

##### Biodistribution of **Antibody**-Liposomes

The biodistribution and blood circulation lifetime of liposomes containing surface-bound **antibodies** was compared to that of liposomes lacking surface-bound **antibodies**. The **antibody**-liposomes were composed of HSPC:CH:PEG hydrazide, at a 2:1:0.1 molar ratio, and sheep IgG covalently linked to PEG chain. Liposomes lacking surface-bound antigens were liposomes composed of HSPC:CH:PEG at a 2:1:0.1 molar ratio and liposomes, composed of HSPC:CH:PEG hydrazide. The average diameter of the liposomes was between 110 and 120 nanometers. For biodistribution studies the liposomes contained <sup>125</sup>I-tyraminylinulin in liposome-entrapped form (Example 2(I)). For blood circulation lifetime studies the liposomes contained <sup>67</sup>Gallium in liposome-entrapped form. The **antibody**-liposomes were prepared as described in Example 1.VIII.

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As shown in Table 1 the biodistribution of liposomes containing **antibody** covalently attached to the end of a PEG chain by a hydrazide group are very similar to those of liposomes containing 30 nonfunctionalized PEG chains. Liposome biodistribution was determined for the blood, liver, spleen, lung, heart and carcass.

of

either 0.2 ml phosphate-buffered saline (PBS) (untreated controls) or with 6 mg/kg of either free DOX, 6 mg/kg of DOX entrapped in HSPC:CH:PEG-DSPE liposomes (liposomal DOX), 6 mg/kg of DOX entrapped in HSPC:CH:PEG-DSPE liposomes containing attached **antibody** 174H.64 (mAb-liposomal DOX) or mAb-liposomes (11-39 Ag mAb) lacking DOX, all in 0.2 ml of sterile saline.

=> d kwic 6

L51 ANSWER 6 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
ABEN Conjugates containing a substance with coagulant activity, such as recombinant Factor IX, non-antigenic polymers, such as **poly(ethylene glycol)**, are disclosed. Also disclosed are methods of forming the novel conjugates of this invention.  
ABFR . . . substance presentant une activite coagulante, tels que le facteur IX de recombinaison, et des polymeres non antigeniques tels que du **poly(ethylene glycol)**; et procedes de preparation de ces nouveaux conjugues.  
DETD . . . to a final concentration of 10 mM and was allowed to sit on ice for 5 minutes, Excess periodate and sucrose were **removed** by desalting on a PD-10 column as described above. A 100 fold excess PEG-



Hydrazide was added, and the reaction proceeded. . . was added to a final concentration of 5 mM and the mixture was kept refrigerated overnight, Excess PEG and NaCNBH4 were **removed** by GPC-HPLC using a Showdex column equilibrated with 0,1 M sodium phosphate pH 7,5, SDS-PAGE of the purified material revealed a. . . 100 mM NaCl with 10 mg/ml glycine, The sample was aliquoted and stored at either 40C, -700C or lyophilized, SDS-PAGE revealed an **increased** and broad molecular weight distribution but no sign of contaminating native protein, Specific activities were \*determined in the presence of Factor IX def. . .

SAMPLE SPECIFIC ACTIVITY (U/mg)

Native Factor IX 47

PEG-F,IX (40C) 128

PEG-F\*IX (-700C) 146

PEG-F,IX (Lyoph) 115

The various embodiments of the present invention,, therefore, provide conjugates which retain significant levels of Factor IX activity while having less of a tendency to cause the formation of inhibitor **antibodies**.

=> d ibib 11

L51 ANSWER 11 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
 ACCESSION NUMBER: 1986004145 PCTFULL ED 20020507  
 TITLE (ENGLISH): PROTEIN MODIFICATION WITH PEG  
 TITLE (FRENCH): MODIFICATION DE PROTEINES AVEC PEG  
 INVENTOR(S): TOMASI, Thomas, B.;  
 ANDERSON, William, L.  
 PATENT ASSIGNEE(S): UNIVERSITY OF NEW MEXICO  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 8604145	A1	19860717

DESIGNATED STATES

W:	DE GB JP
APPLICATION INFO.:	WO 1985-US2572 A 19851231
PRIORITY INFO.:	US 1984-687,811 19841231

=> d kwic 11

L51 ANSWER 11 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN  
 ABEN **PEG**-modified protein molecules characterized by reduced immunogenicity are prepared by covalent modification of the protein with **PEG** employing an active ester intermediate. Antibodies so modified exhibit decreased binding capacity for Fc cell surface receptors, are non-toxic and. . .  
 ABFR Des molecules de proteines modifiees par **PEG** (polyethylene glycol) caracterisees par une immunogenicite reduite sont preparees par modification covalente de la proteine avec **PEG** utilisant un intermediaire d'ester actif. Des anticorps ainsi modifies presentent une capacite de liaison diminuee pour des recepteurs en surface. . .

DETD PROTEIN MODIFICATION WITH PEG

Field--of

Diagnostic and therapeutic procedures of the type dependent upon immunoreaction of **antibody** with a target tissue are frequently hampered by both the immunogenicity of the reagent in clinical applications and binding to cell surface Fc receptors. Immune response to **antibodies** and other foreign proteins, characterized by both allergic phenomena and inactivation of the protein, must be countered by treatment of the protein to obviate stimulation of the host immune system, while retaining desirable protein biologic activity. In addition, it is desirable to increase **antibody** specificity by reduction or elimination of Fc binding to cell surface receptors.

result was obtained in a related study J. \_\_\_\_ T l nnol . hiad mm --l-le-t s.,

327 (1983), wherein it was concluded that PEG-modification of Ig mediated with cyanuric chloride destroyed **antibody** activity.

comprises a polyethylene glycol-protein derivative, and a method for preparing the derivative in excellent yields comprising covalently modifying the protein with polyethylene glycol (PEG) employing an active ester intermediate. Derivatized

**antibodies** are characterized by retained antigen binding activity, low binding capacity for cell surface Fc receptors reduced immunogenicity, good storage stability, and non-toxicity and are . . . such as tumor imaging, chemotherapy, radiotherapy, and immunohistochemical procedures. It is contemplated that a broad range of diagnostic and therapeutic proteins including monoclonal **antibodies** and enzymes, is modifiable by the process of the invention to provide modified proteins having reduced immunogenicity and low non-specific biological . . .

Different symbols depict experiments performed on different days with different samples of PEG-modified **antibody**

An affinity purified rabbit anti-mouse immunoglobulin reagent was modified with FITC to an F/P ratio of 3.7 Qj) A fraction TPIPTOM Qz TRE

According to the invention, immunogenicity of foreign protein, especially **antibody** is reduced or eliminated by covalent

modification of the protein with polyethylene glycol (PEG), employing a PEG active ester intermediate. In contrast to known

prior art modifications, PEG modification of **antibodies** according

to the process of the invention provides a derivative which retains avidity for antigen, while exhibiting reduced immunogenicity. A particular advantage . . . reduction in non-specific binding occurs which

is believed to be attributable to inactivation of the Fc portion of the antibody molecule. The process thus substantially eliminates binding of the **antibody** to cell surface Fc receptors and promotes

**antibody** concentration targeted tissue in applications such

as tumor imaging and immunohistochemical techniques.

Particular **PEG** polymers useful in the process of the invention comprise substituted or unsubstituted **PEG** polymers having molecular weights of from about 1000 to 5000 which are themselves poor immunogens, and which can be coupled to -protein using. . . biologically active and substantially non-toxic and nonimmunogenic. monomethoxypolyethylene glycol (mPEG) satisfies these criteria, and is an especially suitable modifier, particularly for **antibody**. Covalent mPEG modification of **antibody** molecule, using the present active ester approach is accomplished with full retention of binding activity,, and yields very predictable and reproducible modifications.

While the process is particularly useful in reducing the immunogenicity of heterologous species proteins the process is also applicable to homologous species proteins. **Antibodies** are proteins of particular interest, as by the process of the invention, the specificity and avidity of the **antibody** molecules is retained, while non-specific binding of **antibody** molecules to cellular Fc receptor and rapid clearance of the **antibody** from the circulation is obviated. Drugs, toxins, fluorescent, radionuclides, or other active moieties may readily be attached to the modified **antibody** molecule via the **PEG** substituent according to principles understood by those skilled in the art for delivery to selected tissue, especially to tumor tissue for diagnosis or therapy, owing to the decreased non-specific activity of complexes comprising active moieties conjugated with **PEG**-modified **antibody** or other protein, premature dissociation of the complex is avoided and highly selective delivery is achieved.

brief, antisera was applied to the affinity column and the column was washed with 0.5 M sodium thiocyanate and the resulting **antibody** was simultaneously desalted and concentrated using a Micro Pro dialysis apparatus, (Bio Molecular Dynamics Beaverton OR), The purified **antibody** was stored sterile at 4 degrees, -20 degrees. Assay of Anti-Conalbumin Activity and antigen binding activity of the affinity purified and chemical-ly modified **antibodies** was determined by evaluating their ability to competitively inhibit the binding of a rabbit anti-conalbumin-alkaline phosphatase conjugate to conalbumin-coated microtiter plates (Vanguard, Neptune, NJ). The enzyme linked **antibody** for this assay was prepared by a modification of the method described by Avermeas (Immuno. Chem. 5: 43j, 1969) and to assure. . . conalbumin to 10 ug/ml in 0.05 M NaHCO<sub>3</sub> at pH 9.6 and incubating for 18 hours at room temperature, Equal volumes of **antibody** and enzyme conjugate, at the proper dilution, were then incubated in the antigen coated plates with Characterization of Modified **Antibody**. Three different measurements were used to characterize the modified **antibody**. Protein concentration was determined both by optical density measurements at 280 nm, assuming an E<sub>1%</sub><sup>1cm</sup><sub>280nm</sub> = 1.4 for albumin. Immunochem. 2: 343, . . . , 1948) Protein amino groups were determined by TNBS titrations as described by Habeeb (Anal. Biochem. 1: 323, 1966) The extent of **PEG**

modification was also evaluated by measuring an increase in protein size. For this measurement protein size was evaluated using a 0.6% discontinuous. . .

Determination of immunogenicity of

Immunogenicity of rabbit **antibody** and its PEG-modified

derivatives were determined by measuring the **antibody** response of Swiss mice to an intraperitoneal injection of 50 µg of the antigen (rabbit **antibody**) in PBS. The mouse **antibody** response was determined using a two step enzyme linked assay. In brief several two-fold dilutions of mouse sera were incubated on a rabbit. . .

The effect of mPEG modifications, using cyanuric chloride and active ester coupling procedures on **antibody** activity is reported in Table I and II. It is evident from these results that even at low modifications there is a significant decrease in **antibody** binding activity with cyanuric chloride.

Experiments

varying the rate and form of activated PEG along with experiments

varying the reaction time and temperature did not significantly improve the recovery of active **antibody**. In contrast the use of active ester to modify **antibody** with PEG results in no detectable loss in **antibody** titer or **antibody** activity.

TABLE I

Antigen binding of Rat' alumin

Modified with antigen using the, 1;Xanthiric Chloride. Procedure  
% Lysine

Modification mg **Antibody**/mg Protein % Loss of Ab Activity

1\*00 0

0.050 50

0\*15 35

0\*06 94

TABLE II

Activity of Rabbit

Anti-CQ Modified with

ha, rate = 9; Loss of

% Lysine

Modification mg **Antibody**/mg Protein % Loss of Ab Activity

1 0 0 0

1\*0 0

1\*0 0

1\*0 0

100 0

1\*0 0

at ion, o

EXAMPTA.-I-n-, Effectively. Answer Qf

I.--with mPZQ. a lot of,

To verify that **antibody** was significantly modified by this procedure, all mPEG-modified **antibody** preparations were analyzed by SDS gel electrophoresis. An example of one series of derivatives is shown in FIG. 1. Results from this experiment

clearly show that most or all molecules in the population are modified and that the apparent molecular weight increases greatly

following the modification. It should be noted however that the modified **antibodies** tested are a distribution of molecules

each containing different number of **PEG** molecules per **antibody**.

B. The hyperresponsiveness induced by some of the mPEG-modified rabbit **antibodies** in A, gap-ra, was investigated by evaluating the adjuvant properties of **PEG**. Swiss mice were immunized with 50 mg of rabbit immunoglobulin in the presence of varying **PEG** concentrations up to 1 mg/ml **PEG** and the **antibody** response determined fifteen days later. In this experiment the **PEG** was not covalently attached to the rabbit protein.

appear to have an upper limit to the cellular fluorescence intensity whereas cells detected by the reagent that was not mPEG-modified show an **increased** fluorescence intensity (FIG. 7B). It was demonstrated that the mPEG-modified reagent binds to cell surface immunoglobulin whereas the non mPEG-modified reagent exhibits no binding. Immunoglobulin was used to competitively inhibit the binding of both reagents to mouse splenocytes. The results of this experiment, shown in FIG. 8, clearly demonstrate that the binding of the classical fluorescein-antigen complexed reagent (not mPEG-modified) could not be completely inhibited by antigen whereas binding of the mPEG-modified reagent was.

**PEG-modified antibodies** according to the invention exhibit markedly reduced immunogenicity, low specific binding capacity for cell surface Fc receptors, and retention of antigen-binding activity. mPEG modification of **antibodies** also essentially eliminates Fc receptor binding. Covalent modification of more than 15% of amino groups of rabbit anti-conalbumin **antibody** with mPEG completely prevented immune complexes prepared with this **antibody** from binding to the Fc receptor on the murine macrophage cell line P388, D1. Similar sensitivities are observed for mPEG-modified fluorescein labelled **antibodies** since mPEG modification does not quench fluorescein fluorescence. A fluorescein-antigen complexed reagent (not mPEG-modified) could not be completely inhibited by antigen whereas binding of the mPEG-modified reagent was.

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005

E "PEG"/CN 25

L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

L2 185 S L1  
L3 9685 S PEG  
L4 2487 S POLY ( ) ETHYLENE ( ) GLYCOL  
L5 52 S METHOXPOLY ( ) ETHYLENE GLYCOL  
L6 10866 S L5 OR L4 OR L3  
L7 694206 S ANTIBOD?  
L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL  
L9 1041 S L8 AND L6  
L10 129 S L9 AND L7  
L11 7 S ANTI-PEG  
L12 2 S L11 AND L8  
L13 3 S L11 NOT PY>1999  
L14 97 S L10 NOT PY>1999

L15 90 S L14 NOT PY>1998  
 L16 1898836 S INCREASE? OR ACCELERAT?  
 L17 24 S L16 AND L15  
 L18 51664 S L16 (S) L8  
 L19 7 S L18 AND L17

FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005

L20 33476 S PEG  
 L21 12996 S POLY ( ) ETHYLENE ( ) GLYCOL  
 L22 144 S METHOXYPOLY ( ) ETHYLENE GLYCOL  
 L23 41717 S L22 OR L21 OR L20  
 L24 440322 S ANTIBOD?  
 L25 1304988 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
 L26 1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
 L27 3736368 S INCREASE? OR ACCELERAT?  
 L28 99738 S L26 (S) L27  
 L29 1750 S L24 AND L28  
 L30 16 S L29 AND L23  
 L31 9 S ANTI-PEG  
 L32 3 S L31 NOT PY>1999  
 L33 6 S L30 NOT PY>1998

FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005

L34 35377 S PEG  
 L35 5321 S POLY ( ) ETHYLENE ( ) GLYCOL  
 L36 76 S METHOXYPOLY ( ) ETHYLENE GLYCOL  
 L37 80487 S ANTIBOD?  
 L38 492783 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL  
 L39 496097 S INCREASE? OR ACCELERAT?  
 L40 83462 S L38 (S) L39  
 L41 7 S ANTI-PEG  
 L42 5 S L41 AND L40  
 L43 38102 S L34 OR L35 OR L36  
 L44 3934 S L43 (S) L37  
 L45 1413 S L44 AND L40  
 L46 1018 S L44 (P) L40  
 L47 3 S ANTI ( ) (POLYETHYLENE GLYCOL)  
 L48 282 S L46 NOT PY>1999  
 L49 930 S L43/AB  
 L50 12 S L49 AND L48  
 L51 11 S L50 NOT PY>1998

=> file dissab

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MATERIALS OR THEIR USE.

=> s anti-peg

25082 ANTI  
9 ANTIS  
25087 ANTI  
(ANTI OR ANTIS)  
1251 PEG  
154 PEGS  
1334 PEG  
(PEG OR PEGS)  
L52 0 ANTI-PEG  
(ANTI(W) PEG)

=> s anti ( ) (polyethylene glycol)

25082 ANTI  
9 ANTIS  
25087 ANTI  
(ANTI OR ANTIS)  
3287 POLYETHYLENE  
146 POLYETHYLENES  
3344 POLYETHYLENE  
(POLYETHYLENE OR POLYETHYLENES)  
2420 GLYCOL  
177 GLYCOLS  
2537 GLYCOL  
(GLYCOL OR GLYCOLS)  
930 POLYETHYLENE GLYCOL  
(POLYETHYLENE(W) GLYCOL)

L53 0 ANTI (W) (POLYETHYLENE GLYCOL)

=> d his

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